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L1                STR
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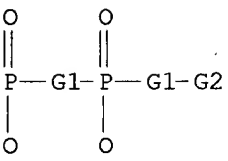

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G1 O,S,CH2,NH
G2 C,H,Ak,Cb

Structure attributes must be viewed using STN Express query preparation.

=> d his

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L1                STRUCTURE UPLOADED
L2             50 L1
L3          25400 L1 SSS FULL
                  E "ETIDRONIC ACID"/CN 25

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     FILE 'REGISTRY' ENTERED AT 08:11:56 ON 27 FEB 2003
                  E "ETIDRONIC ACID"/CN 25
L4               2 S E3 OR E4

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L5            4060 S L4

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                  E "PAMIDRONIC ACID"/CN 25
L6               2 S E2 OR E3

     FILE 'CAPLUS' ENTERED AT 08:12:59 ON 27 FEB 2003
L7             695 S L6

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L8               3 S E3 OR E7 OR E8

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L9              49 S L8

     FILE 'REGISTRY' ENTERED AT 08:14:09 ON 27 FEB 2003
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L11            976 S L10
L12         166817 L3
L13            483 L12 AND (ALZHEIMER## OR AD)

     FILE 'REGISTRY' ENTERED AT 08:17:33 ON 27 FEB 2003


27/02/2003 08:58
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     FILE 'REGISTRY' ENTERED AT 08:30:38 ON 27 FEB 2003
L14          23 S E3 OR E173 OR E174 OR E175 OR E176 OR E178 OR E179 OR E296 OR

     FILE 'CAPLUS' ENTERED AT 08:30:44 ON 27 FEB 2003
L15        8541 S L14
L16       13559 L5 OR L7 OR L9 OR L11 OR L15
L17          19 L16 AND (ALZHEIMER## OR AD)

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     FILE 'CAPLUS' ENTERED AT 08:34:44 ON 27 FEB 2003
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L19           3 L16 AND ALZHEIMER##
L20          21 L18 AND ACETYLCHOLIN?

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     FILE 'CAPLUS' ENTERED AT 08:52:16 ON 27 FEB 2003
                E FREY WILLIAM H/AU 25
L21          37 S (E3 OR E4 OR E7)
                E FAWCETT JOHN R/AU 25
L22          22 S (E3 OR E4 OR E6 OR E7)
                E FREY W/AU 25
L23         158 S (E3 OR E7 OR E8 OR E25 OR E29 OR E30 OR E33)
                E FAWCETT J/AU 25
L24         217 S (E3 OR E13 OR E28 OR E31 OR E32 OR E34 OR E35)
L25         366 L23 OR L24
L26           9 L25 AND L12
L27           1 L25 AND L16
L28           9 L26 OR L27

=> d l28 total ibib abs

L28  ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2001:816459  CAPLUS
DOCUMENT NUMBER:          135:339302
TITLE:                    Methods and compositions for enhancing cellular
                          function through protection of tissue components
INVENTOR(S):              Frey, William H., II; Fawcett, John
                          Randall; Thorne, Robert Gary; Chen, Xueqing
PATENT ASSIGNEE(S):       Healthpartners Research Foundation, USA
SOURCE:                   PCT Int. Appl., 77 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
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     WO 2001082932      A2   20011108       WO 2001-US13931   20010430
     WO 2001082932      A3   20020718
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             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002028786	A1	20020307	US 2001-844450	20010427
EP 1278525	A2	20030129	EP 2001-930957	20010430

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:	US 2000-200843P	P	20000501
	US 2000-230263P	P	20000906
	US 2000-233025P	P	20000915
	US 2000-233263P	P	20000918
	WO 2001-US13931	W	20010430

OTHER SOURCE(S): MARPAT 135:339302

AB Methods and compns. for enhancing cellular function through protection of tissue components, such as receptors, proteins, lipids, nucleic acids, carbohydrates, hormones, vitamins, and cofactors, by administering pyrophosphate analogs or related compds. Preferably, the invention provides a method for protecting a muscarinic acetylcholine receptor (mAChR) an/or increasing the efficacy of and agent the directly or indirectly affects a mAChR in a subject in need thereof.

L28 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1998:318635 CAPLUS
DOCUMENT NUMBER:	129:75495
TITLE:	Synthesis, structure and properties of lanthanide dithionates and their triphenylphosphine oxide complexes
AUTHOR(S):	**Fawcett, John**; Platt, Andrew W. G.; Russell, David R.
CORPORATE SOURCE:	Department of Chemistry, The University Leicester, Leicester, LE1 7RH, UK
SOURCE:	Inorganica Chimica Acta (1998), 274(2), 177-183 CODEN: ICHAA3; ISSN: 0020-1693
PUBLISHER:	Elsevier Science S.A.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB The synthesis and properties of representative lanthanide dithionates are described and their potential use as catalysts discussed from dissociation of the coordinated dithionate in the presence of phosphoryl ligands. Complex formation with OPPh3 was studied and a number of complexes isolated. The IR spectra of all compds. indicate coordination of the dithionate ion to the metal. The x-ray structures of Nd2(S2O6)3·14H2O (R1 = 0.0209 for 3368 diffractometer observed reflections) and Nd2(S2O6)3-(Ph3PO)4·8H2O (R1 = 0.1088 for 5406 diffractometer observed reflections) confirm the coordination of the dithionate with one previously unreported coordination mode, and show a polymeric structure for Nd2(S2O6)3·14H2O while Nd2(S2O6)3(Ph3PO)4·8H2O is a H bonded dimer.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1982:48257 CAPLUS
DOCUMENT NUMBER:	96:48257
TITLE:	Postmortem stability of dopamine-sensitive adenylate cyclase, guanylate cyclase, ATPase, and GTPase in rat striatum
AUTHOR(S):	Nicol, Susan E.; Senogles, Susan E.; Caruso, Thomas P.; Hudziak, James J.; McSwigan, John D.; **Frey**,

William H., II
CORPORATE SOURCE: Dep. Psychiatry, St. Paul-Ramsey Med. Cent., St. Paul, MN, USA
SOURCE: Journal of Neurochemistry (1981), 37(6), 1535-9
CODEN: JONRA9; ISSN: 0022-3042
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The stability of dopamine-sensitive adenylate cyclase, guanylate cyclase, ATPase, and GTPase was measured in homogenates of rat striatal tissue frozen from 0 to 24 postmortem. ATPase, GTPase, and Mg2+-dependent guanylate cyclase activities showed no significant change over this period. Mn2+-dependent guanylate cyclase activity was stable for 10 h postmortem. Basal and dopamine-stimulated adenylate cyclase activity decreased markedly during the 1st 5 h. However, when measured in washed membrane prepns., these adenylate cyclase activities remained stable for ≥10 h. Therefore, the postmortem loss of a soluble activator, such as GTP, may decrease the adenylate cyclase activity in homogenates. These results are not consistent with an earlier suggestion that there is a postmortem degradation of the enzyme itself. Other kinetic parameters of dopamine-sensitive adenylate cyclase can also be measured independently of postmortem changes. Thus, it is possible to investigate kinetic parameters of dopamine-sensitive adenylate cyclase, guanylate cyclase, ATPase, and GTPase in human brain obtained postmortem.

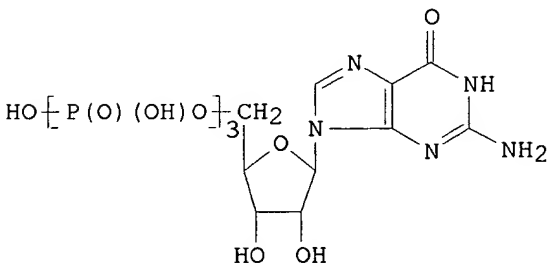
L28 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:204428 CAPLUS
DOCUMENT NUMBER: 94:204428
TITLE: Stimulation of guanylate cyclase by EDTA and other chelating agents
AUTHOR(S): **Frey, William H., II**; Senogles, Susan E.; Tuason, Vicente B.; Nicol, Susan E.
CORPORATE SOURCE: Dep. Psychiatry, St. Paul-Ramsey Med. Cent., St. Paul, MN, 55101, USA
SOURCE: Biochimica et Biophysica Acta (1981), 658(2), 369-76
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The partially purified soluble guanylate cyclase (EC 4.6.1.2) from human caudate nucleus is stimulated 2-4-fold by metal chelating agents. EDTA (K1/2 = 4.8 μM) is more potent than CDTA (K1/2 = 13.2 μM) or EGTA (K1/2 = 21.8 μM) at stimulating activity. Stimulation by chelating agents is apparently not due to removal of inhibitory divalent cations which contaminate the enzyme or reaction mixture EDTA increases guanylate cyclase activity in part by increasing the affinity of the enzyme for the substrate (MgGTP) 10-fold. Dopamine inhibits partially purified guanylate cyclase in the presence or absence of EDTA. Dopamine increases the Ka of guanylate cyclase for the activator, free Mn2+, by >50-fold, from 3 to 150 μM.

L28 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:26717 CAPLUS
DOCUMENT NUMBER: 94:26717
TITLE: Catecholamine-sensitive guanylate cyclase from human caudate nucleus
AUTHOR(S): **Frey, William H., II**; Senogles, Susan E.; Heston, Leonard L.; Tuason, Vicente B.; Nicol, Susan E.
CORPORATE SOURCE: Dep. Psychiatr., St. Paul-Ramsey Med. Cent., St. Paul, MN, 55101, USA

SOURCE: Journal of Neurochemistry (1980), 35(6), 1418-30
CODEN: JONRA9; ISSN: 0022-3042
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Partial purification of soluble guanylate cyclase (I) on DEAE-Sephacel yields 2 sep. peaks of I activity. After 10-fold purification of the soluble I, I is markedly inhibited by micromolar concns. of dopamine (I50 = 0.2 μM). Dopamine inhibition is observed whether the reaction is conducted with Mn2+ or with Mg2+, under air or N2, and using I from either peak from the DEAE-Sephacel column. Other catecholamines also inhibit partially purified I with an order of potency at 1 μM of: dopamine = L-DOPA > norepinephrine = isoproterenol = adrenochrome > epinephrine. The structural requirements for inhibition are 2 free OH groups on the Ph ring and an ethylamine side chain. Dopamine also inhibits the Triton X-100-solubilized microsomal I after partial purification on DEAE-Sephacel. Neither chlorpromazine, propranolol, nor phentolamine at 20 μM effectively blocks the dopamine inhibition of partially purified soluble I. Micromolar concns. of the reducing agents dithiothreitol and glutathione also inhibit partially purified I, but unlike these agents, catecholamines can inhibit whether added in the reduced or the oxidized form. Inhibition of I activity by micromolar concns. of dopamine, adrenochrome, or dithiothreitol is rapidly reversed by dilution and the dopamine inhibition is competitive with MgGTP. Inhibition does not appear to involve covalent binding or to result from the ability of catecholamines to reduce the concns. of O or free radicals in solution

L28 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1980:140832 CAPLUS
DOCUMENT NUMBER: 92:140832
TITLE: Effect of dopamine on activation of rat striatal adenylate cyclase by free magnesium ion and guanyl nucleotides
AUTHOR(S): McSwigan, John D.; Nicol, Susan E.; Gottesman, I. I.; Tuason, V. B.; **Frey, William H., II**
CORPORATE SOURCE: Dep. Psychiatry, St. Paul-Ramsey Med. Cent., St. Paul, MN, 55101, USA
SOURCE: Journal of Neurochemistry (1980), 34(3), 594-601
CODEN: JONRA9; ISSN: 0022-3042
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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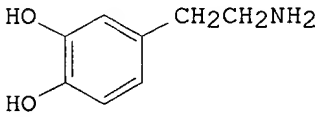

II

AB Stimulation of rat striatal adenylate cyclase [9012-42-4] by guanyl nucleotides was examined utilizing either MgATP or Mg 5'-adenylylimidodiphosphate (MgApp(NH)p) as substrate. GTP (I) [**86-01-1**] and 5'-guanylylimidodiphosphate (Gpp(NH)p) [**34273-04-6**] stimulated adenylate cyclase under conditions where the guanyl nucleotide is not degraded. The apparent stimulation of adenylate cyclase by GDP is due to an ATP-dependent transphorphorylase present in the tissue which convert GDP to I. Apparently, I is the physiol. guanyl nucleotide responsible for stimulation of striatal adenylate cyclase. Dopamine-HCl (II-HCl) [62-31-7] lowered the Ka for Gpp(NH)p stimulation 2-fold, from 2.4 μM to 1.2 μM, and increased maximal velocity 60%. The kinetics of Gpp(NH)p stimulation indicate no homotropic interactions between Gpp(NH)p sites and are consistent with one nonessential Gpp(NH)p activator site per catalytic site. Double reciprocal plots of the activation by free Mg2+ were concave downward, indicating either 2 sets of sites with different affinities or neg. cooperativity (Hill coefficient = 0.3, K0.5 = 23 mM). The data conform well to a model for 2 sets of independent sites, and II lowers the Ka for free Mg2+ at the high-affinity site 3-fold, from 0.21 mM to 0.07 mM. The antipsychotic drug fluphenazine [69-23-8] blocked this shift in Ka due to II. II did not appreciably affect the affinity of adenylate cyclase for the substrate MgApp(NH)p. Thus, II stimulates striatal adenylate cyclase by increasing the affinity for free Mg2+ and guanyl nucleotide and by increasing maximal velocity.

L28 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1978:419162 CAPLUS
DOCUMENT NUMBER: 89:19162
TITLE: The use of the ultracentrifuge to determine the catalytically competent forms of enzymes with more than one oligomeric structure. Multiple reacting forms of pyruvate carboxylase from chicken and rat liver
AUTHOR(S): Taylor, Barry L.; **Frey, William H., II;** Barden, Roland E.; Scrutton, Michael C.; Utter, Merton F.
CORPORATE SOURCE: Dep. Biochem., Case Western Reserve Univ., Cleveland, OH, USA
SOURCE: Journal of Biological Chemistry (1978), 253(9), 3062-9
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The reacting enzyme sedimentation procedure was used to identify the catalytically competent oligomeric forms of pyruvate carboxylases (I) isolated from yeast and from chicken and rat liver. At low protein concns. and with its substrates present, I from chicken liver is a tetramer. However, when concentrated solns. of this enzyme are dialyzed against its substrates, a portion of the enzyme assocs. to a reacting form tentatively identified as an octamer. The activity of both forms is completely dependent on the presence of Ac CoA. I from chicken liver can also form monomers, but no catalytic activity could be demonstrated for this form. In contrast to the chicken liver enzyme, I from rat liver exists as an associating-dissociating mixture of tetramers, dimers, and monomers; all 3 oligomeric forms are catalytically active in the absence of Ac CoA. At low concns. of salt and enzyme, the principal reacting form is the tetramer in the presence of Ac CoA, and the dimer in the absence of the

activator. In high concns. of KHCO3 (0.29M), the predominant form observed soon after mixing is the dimer whether Ac CoA is present or absent. However, incubation in the buffer with high concns. of KHCO3 causes dissociation of the enzyme to monomers which are also catalytically active. I from yeast appears to react as a tetramer in the presence or absence of Ac CoA and no evidence has been obtained from the presence of any stable oligomeric form other than a tetramer.

L28 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1977:67497 CAPLUS
DOCUMENT NUMBER: 86:67497
TITLE: Binding of acetyl-CoA to chicken liver pyruvate carboxylase
AUTHOR(S): **Frey, William H.**; Utter, Merton F.
CORPORATE SOURCE: Sch. Med., Case West. Reserve Univ., Cleveland, OH, USA
SOURCE: Journal of Biological Chemistry (1977), 252(1), 51-6
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pyruvate carboxylase (I) of chicken liver is a tetramer whose catalytic activity is completely dependent on the presence of Ac CoA (II). However, no direct evidence concerning the nature of the binding of II to I has been available. This is due in part to the instability of I and its ability to hydrolyze II at an appreciable rate. The present studies on binding of II show 4 binding sites for II. The binding dissociation constant at pH 7.2 is 13.9 μM as compared with an activation constant of 13.3 μM for the catalytic reaction at this pH. The relation between II concentration and catalytic activity is highly cooperative. The binding process also exhibits pos. cooperativity but to a lower degree. I is rapidly inactivated and dissociated in the cold (0°). The inactive protomeric form of I was unable to bind II at 0° although the tetrameric species can do so. These results provide a plausible explanation for the catalytic inactivity of the protomer. The presence of II results in an UV difference spectrum for I with a maximum at 280 nm. Half-maximum optical d. difference is observed at an II concentration of 9 μM, in reasonable agreement with the binding and activation consts.

L28 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1975:574650 CAPLUS
DOCUMENT NUMBER: 83:174650
TITLE: Mechanism of acetyl-CoA activation of pyruvate carboxylase
AUTHOR(S): **Frey, William H., II**
CORPORATE SOURCE: Case West. Reserve Univ., Cleveland, OH, USA
SOURCE: (1975) 175 pp. Avail.: Xerox Univ. Microfilms, Ann Arbor, Mich., Order No. 75-19,206
From: Diss. Abstr. Int. B 1975, 36(3), 1189-90
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

=> d l19 total ibib abs

L19 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:833023 CAPLUS
DOCUMENT NUMBER: 135:376738
TITLE: Compounds and methods for modulating cerebral amyloid angiopathy using inhibitors of an amyloid β peptide
INVENTOR(S): Green, Allan M.; Gervais, Francine
PATENT ASSIGNEE(S): Neurochem, Inc., Can.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

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WO 2001085093	A2	20011115	WO 2000-IB2078	20001222
WO 2001085093	A3	20020829		
WO 2001085093	C2	20020926		
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EP 1251837	A2	20021030	EP 2000-993855	20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2000016652	A	20021119	BR 2000-16652	20001222
US 2003003141	A1	20030102	US 2000-747408	20001222

PRIORITY APPLN. INFO.: US 1999-171877P P 19991223
WO 2000-IB2078 W 20001222

OTHER SOURCE(S): MARPAT 135:376738

AB The invention provides methods of inhibiting cerebral amyloid angiopathy (CAA) and treating a disease state characterized by cerebral amyloid angiopathy, e.g., **Alzheimer**'s disease, in a subject using an inhibitor of the 39-40 amino acid amyloid β peptide (Aβ40). The Aβ40 inhibitor is selected from, e.g., sulfonic acid derivs., such as ethanesulfonic acid, 1,2-ethanedisulfonic acid, 1-propanesulfonic acid, 1,3-propanedisulfonic acid, 1,4-butanedisulfonic acid, 1,5-pentanedisulfonic acid, 2-aminoethanesulfonic acid, 4-hydroxy-1-butanesulfonic acid, 1-butanesulfonic acid, 1-decanesulfonic acid, 2-propanesulfonic acid, 3-pentanesulfonic acid, 4-heptanesulfonic acid, etc., and pharmaceutically acceptable salts thereof or from from phosphonic acid derivs., such as diethylphosphonoacetic acid, phenylphosphonic acid, 3-aminopropylphosphonic acid, propylphosphonic acid, etc. The compds. are formulated in a dispersion system, a liposome formulation, or microspheres using a polymeric matrix. The polymeric matrix is selected from natural polymers, such as albumin, alginate, cellulose derivs., collagen, fibrin, gelatin, and polysaccharides, or synthetic polymers such as polyesters, polyethylene glycol, poloxamers,

and polyanhydrides. For example, the ability of compds. of the invention to inhibit CAA was measured in 9 wk old hAPP transgenic mice treated with two different concns. of a compound of the present invention, 3-amino-1-propanesulfonic acid sodium salt, 100 and 30 mg/kg. Mice were administered the compound for 8 wk, after which they were sacrificed and their brains were perfused and processed for histol. staining with Thioflavin S. This method may also be used as a screening method for determining activity of a candidate compound for inhibiting CAA. The extent of CAA in brain sections obtained from these animals was qual. determined following staining. The results indicate that the test compound was effective in (i) reducing the number of mice showing CAA, and (ii) showing an effect on the severity of the deposition seen in the brain vasculature of these animals.

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:816459 CAPLUS
DOCUMENT NUMBER: 135:339302
TITLE: Methods and compositions for enhancing cellular function through protection of tissue components
INVENTOR(S): Frey, William H., II; Fawcett, John Randall; Thorne, Robert Gary; Chen, Xueqing
PATENT ASSIGNEE(S): Healthpartners Research Foundation, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001082932	A2	20011108	WO 2001-US13931	20010430
WO 2001082932	A3	20020718		
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US 2002028786	A1	20020307	US 2001-844450	20010427
EP 1278525	A2	20030129	EP 2001-930957	20010430
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:
US 2000-200843P P 20000501
US 2000-230263P P 20000906
US 2000-233025P P 20000915
US 2000-233263P P 20000918
WO 2001-US13931 W 20010430

OTHER SOURCE(S): MARPAT 135:339302

AB Methods and compns. for enhancing cellular function through protection of tissue components, such as receptors, proteins, lipids, nucleic acids, carbohydrates, hormones, vitamins, and cofactors, by administering pyrophosphate analogs or related compds. Preferably, the invention provides a method for protecting a muscarinic acetylcholine receptor (mAChR) an/or increasing the efficacy of and agent the directly or indirectly affects a mAChR in a subject in need thereof.

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:559016 CAPLUS
DOCUMENT NUMBER: 97:159016
TITLE: Aluminum-27 NMR studies of aluminum(III)-phosphate complexes in aqueous solution
AUTHOR(S): Karlik, S. J.; Elgavish, G. A.; Pillai, R. P.; Eichhorn, G. L.
CORPORATE SOURCE: Gerontol. Res. Cent., Natl. Inst. Aging, Baltimore, MD, 21224, USA
SOURCE: Journal of Magnetic Resonance (1969-1992) (1982), 49(1), 164-7
CODEN: JOMRA4; ISSN: 0022-2364
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The use of 27Al-NMR to probe the interaction of Al with a variety of phosphate ligands (orthophosphate, diphosphate, triphosphate, AMP, cAMP, ADP, CDP, ATP, dATP, GTP, CTP, and NADP) in aqueous solution is described. The complexes of these ligands with Al existed in slow exchange with Al(H2O)63+ on the 27Al-NMR time scale and could be observed as peaks that were distinct from the resonance of free Al. The upper limit of the exchange rates between the various Al complexes ranged 7-23 + 102 s-1. All phosphate ligands induced upfield shifts of 3-7 ppm in the 27Al-NMR spectra. The affinity of the ligands for Al increased with the number of phosphate groups present, and nucleotides bound Al more weakly than the corresponding inorg. phosphate esters. The study of interaction of Al with nucleotides and other phosphate ligands may be important for understanding the role of Al3+ in e.g. **Alzheimer**'s disease and dialysis encephalopathy.

=> d l20 total ibib abs

L20 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:419306 CAPLUS
DOCUMENT NUMBER: 137:245372
TITLE: The brain insulin signal transduction system and sporadic (type II) **Alzheimer** disease: An update
AUTHOR(S): Hoyer, S.
CORPORATE SOURCE: Department of Pathochemistry and General Neurochemistry, University of Heidelberg, Germany
SOURCE: Journal of Neural Transmission (2002), 109(3), 341-360
CODEN: JNTRF3; ISSN: 1435-1463
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Nosol., **Alzheimer** disease may not be considered to be a single disorder in spite of a common clin. phenotype. Only a small proportion of about 5% to 10% of all **Alzheimer** cases is due to genetic mutations (type I) whereas the great majority of patients was found to be sporadic in origin. It may be assumed that susceptibility genes along with lifestyle risk factors contribute to the causation of the age-related sporadic **Alzheimer** disease (type II). In this context, the desensitization of the neuronal insulin receptor similar to not-insulin dependent diabetes mellitus may be of pivotal significance. This abnormality along with a reduction in brain insulin concentration is assumed to induce a cascade-like process of disturbances including cellular glucose,

acetylcholine, cholesterol, and ATP associated with abnormalities in membrane pathol. and the formation of both amyloidogenic derivs. and hyperphosphorylated tau protein. Sporadic **Alzheimer** disease may, thus, be considered to be the brain type of diabetes mellitus II. Exptl. evidence is provided and discussed.

REFERENCE COUNT: 140 THERE ARE 140 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107671 CAPLUS
DOCUMENT NUMBER: 136:163667
TITLE: Methods for biosensor library synthesis and applications of use
INVENTOR(S): Minshull, Jeremy; Davis, S. Christopher; Welch, Mark; Raillard, Sun Ai; Vogel, Kurt; Krebber, Claus
PATENT ASSIGNEE(S): Maxygen, Inc., USA
SOURCE: PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002010750	A2	20020207	WO 2001-US24182	20010731
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002102577	A1	20020801	US 2001-920452	20010731
US 2002127623	A1	20020912	US 2001-920607	20010731

PRIORITY APPLN. INFO.: US 2000-222056P P 20000731
US 2000-244764P P 20001031

AB The invention concerns methods for sensing test stimuli using arrays of biopolymers. Reusable library arrays of biopolymers, such nucleic acid variants, and expression products encoded by nucleic acid variants are provided. The present invention provides novel methods for detecting a wide range of biol., chem. and biochem. stimuli. The methods of the invention utilize biopolymers and arrayed libraries of biopolymers, members of which are capable of binding the biol., chem. or biochem. stimuli, and upon binding produce a detectable signal. Upon contact with the test stimulus, a test stimulus array pattern is produced and detected. The test stimulus array pattern is then compared to the calibrating array pattern enabling identification of the test stimulus. Examples provide extensive listings of suitable hormones and enzymes suitable for such biosensor development. Diagrams describing the apparatus are given.

L20 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:816459 CAPLUS
DOCUMENT NUMBER: 135:339302
TITLE: Methods and compositions for enhancing cellular function through protection of tissue components

INVENTOR(S): Frey, William H., II; Fawcett, John Randall; Thorne, Robert Gary; Chen, Xueqing
PATENT ASSIGNEE(S): Healthpartners Research Foundation, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001082932	A2	20011108	WO 2001-US13931	20010430
WO 2001082932	A3	20020718		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002028786	A1	20020307	US 2001-844450	20010427
EP 1278525	A2	20030129	EP 2001-930957	20010430
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:

US 2000-200843P	P	20000501
US 2000-230263P	P	20000906
US 2000-233025P	P	20000915
US 2000-233263P	P	20000918
WO 2001-US13931	W	20010430

OTHER SOURCE(S): MARPAT 135:339302

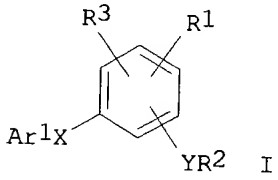
AB Methods and compns. for enhancing cellular function through protection of tissue components, such as receptors, proteins, lipids, nucleic acids, carbohydrates, hormones, vitamins, and cofactors, by administering pyrophosphate analogs or related compds. Preferably, the invention provides a method for protecting a muscarinic **acetylcholine** receptor (mAChR) an/or increasing the efficacy of and agent the directly or indirectly affects a mAChR in a subject in need thereof.

L20 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:816444 CAPLUS
DOCUMENT NUMBER: 135:352829
TITLE: Combination therapeutic compositions containing benzene compounds
INVENTOR(S): Jaen, Juan C.; Chen, Jin-Long
PATENT ASSIGNEE(S): Tularik Inc., USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001082916	A2	20011108	WO 2001-US14393	20010502
WO 2001082916	A3	20020704		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002037928 A1 20020328
PRIORITY APPLN. INFO.: US 2001-847887 20010502
US 2000-201613P P 20000503
OTHER SOURCE(S): MARPAT 135:352829
GI



I

AB The present invention provides pharmaceutical compns. and methods for the treatment of diabetes mellitus using combination therapy. The compns. relate to a benzene compound and an antidiabetic agent such as sulfonylureas, biguanides, glitazones, α-glucosidase inhibitors, potassium channel antagonists, aldose reductase inhibitors, glucagon antagonists, activators of RXR, insulin therapy or other anti-obesity agent. The methods include the administration of the combination of benzene compound with antidiabetic agent where the two components are delivered in a simultaneous manner, where the benzene compound is administered first, followed by the antidiabetic agent, as well as wherein the antidiabetic agent is delivered first followed by the benzene compound For example, the benzene compound (I) was synthesized using a 5-amino-2-(3-chloro-5-pyridyloxy)benzonitrile (0.457 g) in methylene chloride to which was added 2,4-dichlorobenzenesulfonyl chloride (0.456 g), followed by pyridine (150 μL). The reaction progress was monitored by TLC, and upon completion the solvent was removed under vacuum. The resulting residue was partitioned between methylene chloride and water. The organic layer was drawn off and concentrated The residue was triturated with ether to provide 0.447 g of I as a white solid, m.p. 154-156°.

L20 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:720164 CAPLUS
DOCUMENT NUMBER: 137:56694
TITLE: Treatment of cognitive dysfunction associated with **Alzheimer**'s disease with cholinergic precursors. Ineffective treatments or inappropriate approaches?
AUTHOR(S): Amenta, F.; Parnetti, L.; Gallai, V.; Wallin, A.
CORPORATE SOURCE: Department of Pharmacological Sciences and Experimental Medicine, Clinical Research Unit, University of Camerino, Camerino, 62032, Italy
SOURCE: Mechanisms of Ageing and Development (2001), 122(16), 2025-2040
CODEN: MAGDA3; ISSN: 0047-6374

PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The observations of the loss of cholinergic function in neocortex and hippocampus in **Alzheimer**'s disease (AD) developed the hypothesis that replacement of cholinergic function may be of therapeutic benefit to AD patients. The different approaches proposed or tested included intervention with **acetylcholine** (ACh) precursors, stimulation of ACh release, use of muscarinic or nicotinic receptor agonists and **acetylcholinesterase** (AChE) or cholinesterase (ChE) inhibition. Inhibition of endogenous ACh degradation through ChE inhibitors and precursor loading were treatments more largely investigated in clin. trials. Of the numerous compds. in development for the treatment of AD, AChE and ChE inhibitors are the most clin. advanced, although clin. trials conducted to date did not always confirm a significant benefit of these drugs on all symptom domains of AD. The first attempts in the treatment of AD with cholinergic precursors did not confirm a clin. utility of this class of compds. in well controlled clin. trials. However, cholinergic precursors most largely used such as choline and phosphatidylcholine (lecithin) were probably not suitable for enhancing brain levels of ACh. Other phospholipids involved in choline biosynthetic pathways such as CDP-choline, choline alphoscerate and phosphatidylserine clearly enhanced ACh availability or release and provided a modest improvement of cognitive dysfunction in AD, these effects being more pronounced with choline alphoscerate. Although some pos. results cannot be generalized due to the small nos. of patients studied, they probably would justify reconsideration of the most promising mols. in larger carefully controlled trials.

REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:300716 CAPLUS
DOCUMENT NUMBER: 134:320882
TITLE: Allosteric sites on muscarinic receptors, and use in compound screening
INVENTOR(S): Birdsall, Nigel; Lazareno, Sebastian
PATENT ASSIGNEE(S): Medical Research Council Technology, UK
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001029036	A2	20010426	WO 2000-GB4064	20001020
WO 2001029036	A3	20020510		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1222463	A2	20020717	EP 2000-971543	20001020

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

PRIORITY APPLN. INFO.: GB 1999-24962 A 19991021
WO 2000-GB4064 W 20001020

OTHER SOURCE(S): MARPAT 134:320882

AB An allosteric site on muscarinic receptors is disclosed, together with its use for screening for compds. capable of modulating the binding of a primary ligand such as **acetylcholine** to the receptor. The site is characterized herein by a series of indolocarbazoles and related compds. These compds. are capable of binding to the allosteric site to modulate the binding of a primary ligand to the receptors, showing pos., neg. and neutral cooperativity and selectivity for muscarinic receptor subtypes.

L20 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:70303 CAPLUS
DOCUMENT NUMBER: 135:17575
TITLE: Apolipoprotein E and **Alzheimer**'s disease: A role in amyloid catabolism
AUTHOR(S): Poirier, Judes
CORPORATE SOURCE: The Centre for Studies in Aging, McGill University, Montreal, QC, H4H 1R3, Can.
SOURCE: Annals of the New York Academy of Sciences (2000), 924(Alzheimer's Disease), 81-90
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 32 refs. It has been shown over the past few years that apolipoprotein E (apoE) plays a central role in the brain response to injury and neurodegeneration in mammalian species. The coordinated expression of apoE and its different receptors, the so-called LDL receptor family, appears to regulate the transport of cholesterol and phospholipids during the early and middle phases of the reinnervation in the adult mammalian brain. As neurons undergo dendritic remodelling and synaptogenesis using cholesterol internalization through the apoE/LDL receptor pathway, they progressively shut down 3,3-hydroxymethylglutaryl-CoA (HMG CoA) reductase activity, the rate-limiting enzyme in the synthesis of cholesterol. These results suggest that cholesterol delivery and synthesis in the brain are tightly regulated through an apoE-dependent mechanism. The discovery that the apolipoprotein e4 allele is strongly linked to both sporadic and familial late-onset **Alzheimer**'s disease (AD) has raised the possibility that a dysfunction of lipid transport could explain the poor compensatory synaptogenesis reported by several independent research groups in the brain of AD subjects. Recently, it has been shown that alterations of cholesterol homeostasis in the brain by exogenous administration of dietary cholesterol, or through inhibition of cholesterol synthesis, markedly affect beta amyloid production (1-40 and 1-42) and deposition and significantly impair amyloid precursor protein (APP) metabolism In vivo, it has been shown that breeding of APP-overexpressing mice with apoE knockout mice completely abolishes amyloid plaque deposition in the brain of hybrid animals, without affecting beta amyloid steady state levels. Conversely, introduction of the human apoE3 and apoE4 genes in APP-overexpressing mice drastically reduced beta amyloid deposition in the brain of hybrid mice, confirming the proposed biol. role of apoE in the clearance of extracellular beta amyloid. These results indicate that lipid homeostasis is controlled in large part by the apoE lipoprotein transport system in the extracellular space, whereas alterations in intracellular lipid homeostasis markedly

affect APP processing, beta amyloid production and plaque formation in vivo. The convergence of the so-called amyloid cascade hypothesis (Hardy et al., 1992) and of the apoE/lipid recycling cascade model (Poirier, 1994) is consistent with the notion that alterations in lipid homeostasis could serve as the common denominator for apoE and beta amyloid dysfunctions in **Alzheimer**'s disease. It is also interesting to note that lipid homeostasis is also a central feature of one of the most important neurotransmitter systems in the brain: the cholinergic system. This system is unique in the CNS since it relies heavily on lipid bioavailability to locally synthesize **acetylcholine**. It is thus quite tempting to propose that two of the most common neuropathol. landmarks of AD - namely, cholinergic dysfunction and amyloid deposition - may in fact depend on the integrity of local lipid homeostatic processes, which in turn are strongly dependent upon proper lipid delivery by the apoE transport system.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:743679 CAPLUS

DOCUMENT NUMBER: 134:51714

TITLE: Neural nicotinic receptors: Interaction with purine receptors

AUTHOR(S): Diaz-Hernandez, Miguel; Gualix, Javier; Gomez-Villafuertes, Rosa; Castro, Enrique; Pintor, Jesus; Teresa, Y. M.

CORPORATE SOURCE: Miras-Portugal, Departmento de Bioquimica, Facultad de Veterinaria, Universidad Complutense., Madrid, 28040, Spain

SOURCE: Anales de la Real Academia de Farmacia (2000), 66(2), 165-183
CODEN: ARAFAY; ISSN: 0034-0618

PUBLISHER: Real Academia de Farmacia

DOCUMENT TYPE: Journal

LANGUAGE: Spanish

AB Nicotine is a volatile alkaloid that interacts with the ionotropic **acetylcholine** receptors, thus named nicotinic receptors. The nicotinic receptors are very abundant at the Torpedo elec. organ cholinergic synapses, allowing their characterization. These receptors are analogous to the mammalian neuromuscular junction, they are pentameric and contain five subunits, two α, and one of each other (2α1, β1, γ, δ). The protein family of α subunits contain 9 members, and that of β subunits four members. Their combinations originate a large number of different receptors with specific distribution in the nervous system. Neural nicotinic receptors can be classified in two main groups, the first one are receptors inhibited by α-bungarotoxin and containing exclusively the α7 and α8 subunits, originating homomeric receptors (5α7 or 5α8). The second group of neural nicotinic receptors is not sensitive to α-bungarotoxin, but they are activated by epibatidine. They contain a larger variety of α and β subunits and the combination α4/β2 is very frequent. Both neural nicotinic receptors when stimulated allow the Ca2+ and Na+ entrance, originating a membrane depolarization and subsequently the exocytotic release of neurotransmitters. Nicotinic receptors are widely distributed in mammalian brain, and their localization in nerve terminals is mainly presynaptic. There, they facilitate, potentiate or induce the neurotransmitter release of the **acetylcholine** itself, or other neurotransmitters, such as glutamate, noradrenaline or GABA. Special

mention deserves the facilitation of dopamine release from striatum/nucleus accumbens that provide a plausible explanation on tobacco smoking addiction. This wide effect on secretion potentiation carried out by **acetylcholine** via nicotinic receptors could explain the fatal consequences derived from the cholinergic neurons lost, as it is the case in **Alzheimer** disease. The presence of nicotinic receptors in isolated nerve terminals was studied by microfluorescence coupled to video imaging, measuring the Ca2+ entrance with a fluorescent die, as it was also done for the ATP and ApnA ionotropic receptors. At the same terminals by immunohistochem. studies, the presence of the P2X3, subtype of ATP receptors was shown. ATP and Ap5A were able to induce the release of **acetylcholine** from rat midbrain synaptic terminals. These results corroborate the idea of a certainly complex cross-talk between nucleotide and nicotinic receptors at the same presynaptic terminals, with relevant consequences for neural functioning and future pharmacol.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:74658 CAPLUS

DOCUMENT NUMBER: 132:102759

TITLE: Double-blind placebo-controlled study with citicoline in APOE genotyped **Alzheimer**'s disease patients. Effects on cognitive performance, brain bioelectrical activity and cerebral perfusion

AUTHOR(S): Alvarez, X. A.; Mouzo, R.; Pichel, V.; Perez, P.; Laredo, M.; Fernandez-Novoa, L.; Corzo, L.; Zas, R.; Alcaraz, M.; Secades, J. J.; Lozano, R.; Cacabelos, R.

CORPORATE SOURCE: EuroEspes Biomedical Research Center, Barcelona, Spain

SOURCE: Methods and Findings in Experimental and Clinical Pharmacology (1999), 21(9), 633-644
CODEN: MFEPDX; ISSN: 0379-0355

PUBLISHER: Prous Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cytidine 5'-diphosphocholine (citicoline) is a an endogenous intermediate in the biosynthesis of structural membrane phospholipids and brain **acetylcholine**. Citicoline has been extensively used for the treatment of neurodegenerative disorders associated with head trauma, stroke, brain aging, cerebrovascular pathol. and **Alzheimer**'s disease. In this study we have investigated the efficacy and safety of the treatment with citicoline vs. placebo in patients with **Alzheimer** disease. Thirty patients (age = 73.0±8.5 yr; range = 57-87 yr) with mild to moderate senile dementia (GDS: stages 3-6) of the **Alzheimer** type were included in a double-blind, randomized and placebo-controlled clin. trial. After a 2-wk period of drug washout, patients were treated with (i) placebo (n = 17; age = 73±5 yr) or (ii) 1,000 mg/day of citicoline (n = 13; age = 76±9 yr) for 12 wk (84 days). Examns. were done at baseline (T0) and after the 12 wk of treatment (T12). As compared to placebo, citicoline improved cognitive performance in **Alzheimer**'s disease patients with APOE E4 (ADAS: difference between groups = -3.2±1.8 scores, $p < 0.05$; ADAS-cog: difference between groups = -2.3±1.5, ns); and this improvement on cognition was more pronounced (ADAS, $p < 0.01$; ADAS-cog: difference between groups = -2.8±1.3, $p < 0.06$) in patients with mild dementia (GDS < 5). Citicoline also increased cerebral blood flow velocities in comparison with placebo ($p < 0.05$) when transcranial Doppler recordings from both hemispheres were considered together, as well as diastolic velocity in the left middle cerebral artery ($p < 0.05$). Patients treated with citicoline

showed an increase in the percentage of brain bioelec. activity of α (occipital electrodes) and θ type (left side electrodes), accompanied by a decrease in relative delta activity particularly marked in the left temporal lobe. Significant differences with respect to placebo ($p < 0.05$) were observed for θ activity in several fronto-parieto-temporal electrodes of the left hemisphere. Treatment with citicoline tended to reduce serum IL-1β levels, mainly after 4 wk of administration, with no modified blood histamine content. In addition, neither adverse side effects nor alterations in biol. and hematol. parameters were induced by citicoline. The present data indicate that citicoline (1.000 mg/day) is well tolerated and improves cognitive performance, cerebral blood perfusion and the brain bioelec. activity pattern in AD patients. According to our results, it seems that citicoline might be a useful treatment in **Alzheimer**'s disease, and that the efficacy of this compound is greater in patients with mild mental deterioration and/or bearing the ε4 allele of the APOE.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:452513 CAPLUS
DOCUMENT NUMBER: 132:48493
TITLE: Reduced high-affinity agonist binding at the M1 muscarinic receptor in **Alzheimer**'s disease brain: differential sensitivity to agonists and divalent cations
AUTHOR(S): Ladner, Christopher J.; Lee, John M.
CORPORATE SOURCE: Department of Pharmacology, Loyola University Chicago, Maywood, IL, 60153, USA
SOURCE: Experimental Neurology (1999), 158(2), 451-458
CODEN: EXNEAC; ISSN: 0014-4886
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB M1 muscarinic **acetylcholine** receptor (M1AchR)-G protein coupling, as measured by high-affinity agonist binding, was examined in membranes prepared from postmortem human temporal cortex (Brodmann area 38) from individuals with **Alzheimer**'s disease (AD) and age-matched controls. Binding competitions between the M1AchR-selective antagonist [3H]pirenzepine ([3H]PZ) and muscarinic agonists carbachol, **acetylcholine**, oxotremorine, and oxotremorine M were conducted. In the presence of 1 mM $MgCl_2$, the inhibition of [3H]PZ binding by carbachol, **acetylcholine**, or oxotremorine M was best described by a two-affinity state model for control and AD cases, whereas oxotremorine binding affinity was best fit to a single-state model. Although both control and AD groups had similar KD values for the high- and low-affinity agonist-binding sites, the proportion of M1AchRs exhibiting high affinity for carbachol and **acetylcholine** was reduced by 48 and 33%, resp., in AD membranes relative to controls. No changes in the binding of the oxotremorine M or oxotremorine were noted. The nonhydrolyzable guanine nucleotide GppNHp (100μM) reduced the proportion of M1AchRs with high affinity for agonists in both control and AD membranes. Substitution of 1 mM $MnCl_2$ for $MgCl_2$ restored high-affinity carbachol binding at the M1AchR in AD membranes similar to that seen in controls. In the presence of 1 mM $MnCl_2$, agonist binding in controls did not differ from 1 mM $MgCl_2$. In the absence of cations (1 mM EDTA), no differences between control and AD M1AchR carbachol binding were observed Thus, the loss of high-affinity agonist binding at the M1AchR in AD is dependent on the agonist and cation studied.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:258276 CAPLUS
DOCUMENT NUMBER: 129:52716
TITLE: Possible role of tau protein kinases in pathogenesis of **Alzheimer**'s disease
AUTHOR(S): Imahori, K.; Hoshi, M.; Ishiguro, K.; Sato, K.; Takahashi, M.; Shiurba, R.; Yamaguchi, H.; Takashima, A.; Uchida, T.
CORPORATE SOURCE: Mitsubishi Kasei Institute of Life Sciences, Tokyo, 194, Japan
SOURCE: Neurobiology of Aging (1998), 19(Suppl. 1, Proceedings of the 11th Annual Tokyo Institute of Psychiatry International Symposium, 1997), S93-S98
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 23 refs. Tau protein kinases (TPK) I and II were isolated as candidate enzymes responsible for the hyperphosphorylation observed in PHF-τ. Four phosphorylation sites of tau were identified for each kinase, accounting for most, but not all, of the major phosphorylation sites of PHF-τ. Immunostaining with anti-TPK1 antibody indicated that this kinase is up-regulated in AD brain. Such up-regulation of TPK1 and phosphorylation of tau were reproduced by treating cultured hippocampal cells with amyloid β (Aβ) protein. In addition, we found that TPK1 can phosphorylate and inactivate pyruvate dehydrogenase (PDH), which is expected to result in depletion of acetyl-CoA, a key substrate of **acetylcholine** synthesis, Indeed, when septum cells were treated with Aβ, the level of **acetylcholine** decreased dramatically.

L20 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:92997 CAPLUS
DOCUMENT NUMBER: 128:213262
TITLE: Citicoline antagonizes bromazepam-induced amnesia in rats
AUTHOR(S): Alvarez, X. Anton; Vecino, Begona; Perea, Juan Enrique; Daniele, Danilo; Cacabelos, Ramon
CORPORATE SOURCE: EuroEspes Biomedical Research Center, A Coruna, 15166, Spain
SOURCE: Human Psychopharmacology (1997), 12(6), 547-556
CODEN: HUPSEC; ISSN: 0885-6222
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Citicoline is an endogenous intermediate in the biosynthesis of brain phospholipids and **acetylcholine** used for the treatment of neurodegenerative processes associated with head trauma, stroke, brain aging, cerebrovascular pathol. and **Alzheimer**'s disease. In this study the authors have investigated the effects of citicoline on acquisition and retention in passive avoidance and spatial discriminative learning tasks in control rats and in bromazepam-treated animals. Interactions of citicoline with bromazepam on exploratory behavior (anxiolytic/sedative activity) and motor co-ordination (myorelaxing activity) were also evaluated to test the specificity of the cognitive effects of citicoline. The authors' results indicate that citicoline reverses bromazepam-induced amnesia, improves retention in control rats, and has no significant

effects on spontaneous activity and motor co-ordination when given alone or in combination with bromazepam. According to these results the authors conclude that citicoline acts as a promnesic and anti-amnesic drug with no sedative-myorelaxing activity in rats. Therefore, this compound might be of use for the specific treatment of cognitive impairments associated with the chronic use of benzodiazepines.

L20 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:227733 CAPLUS
DOCUMENT NUMBER: 126:291921
TITLE: Neuronal cell death via TPK I-in vitro model of **Alzheimer** disease
AUTHOR(S): Ishiguro, Koichi; Hoshi, Minako; Takashima, Akihiko
CORPORATE SOURCE: Mitsubishi Kasei Inst. Life Sciences, Tokyo, 194, Japan
SOURCE: Shinkei Kenkyu no Shinpo (1997), 41(1), 105-114
CODEN: SKNSAF; ISSN: 0001-8724
PUBLISHER: Igaku Shoin
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Histopathol. features of **Alzheimer**'s disease (AD) include extracellular deposits of amyloid β (Aβ) fibril in the cores of senile plaques, intracellular neurofibrillary tangles (NFT) which are composed of paired helical filaments (PHF), and neuronal cell loss. The main component of PHF is highly phosphorylated tau protein. The authors identified a protein kinase converting normal tau into PHF-like state. The kinase is tau protein kinase (TPK) I/glycogen synthase kinase (GSK)-3β. Using neuronal cell culture system as AD model, it has been realized that TPK I/GSK-3β plays a central role in AD pathol. According to the amyloid hypothesis for the pathogenesis of AD, Aβ has directly contributes to neurodegeneration and formation of NFT. In fact, Aβ treatment induces hyperphosphorylation of tau and neuronal death in primary cultures of embryonic rat hippocampal neurons. GSK-3β was implicated by expts. in which the Aβ toxicity was prevented by pretreatment of the cells with antisense DNA for TPK I/GSK-3β. Treatment of cells with Aβ activated TPK I/GSK-3β, concomitantly with inactivation of phosphatidyl inositol-3 kinase (PI-3 kinase). An inhibitor of PI-3 kinase, wortmannin, activated TPK I/GSK-3β, enhanced tau phosphorylation and increased neuronal cell death. These results suggest that inhibition of PI-3 kinase is involved in the cascade of Aβ toxicity. Aβ treatment also induces disruption of axonal transport of amyloid precursor protein (APP) derivs. and then its cytoplasmic accumulation, which may be similar to APP over expression that causes neuronal death. TPK I/GSK-3β antisense DNA have been found to block the effects. The observed accumulation of APP in the cytoplasm of these cells may be the result of destabilizing effects of hyperphosphorylated tau on microtubule arrays. Screening of TPK I/GSK-3β-binding proteins with two-hybrid system revealed that pyruvate dehydrogenase (PH) is one such protein. TPK I/GSK-3β phosphorylates and inactivates PDH in vitro. In cultured neurons, PDH was inactivated in inverse proportion to the Aβ-induced TPK I/GSK-3β activation. PDH activity was recovered by blocking of TPK I/GSK-3β synthesis. In cultures of cholinergic neurons, Aβ treatment induced impairment of **acetylcholine** synthesis, one of features of AD brain. These results suggest that TPK I/GSK-3β also participates in decreases in energy metabolism and **acetylcholine** synthesis via PDH inactivation. Taken together, the results suggest that TPK I/GSK-3β plays a central role in abnormal phosphorylation of tau and amyloid toxicity in the pathogenesis of AD. The authors' current working

hypothesis of Aβ -induced neuronal cell death is in the following. Aβ inactivates PI-3 kinase and activates TPK I/GSK-3β, which in turn phosphorylates and inactivates both tau and PDH. After the ability of tau to promote microtubule assembly is diminished by phosphorylation, soluble tau mols. aggregate into PHF by an unknown mechanism. Destabilization of microtubule arrays causes inhibition of axonal transport and accumulation of APP. Phosphorylation of PDH inhibits the reaction converting pyruvate to acetyl-CoA, resulting in inhibition of energy metabolism and a decrease in **acetylcholine**. These changes may lead to neuronal cell death.

L20 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:524248 CAPLUS
DOCUMENT NUMBER: 125:158647
TITLE: Method of treating amyloidosis by modulation of calcium
INVENTOR(S): Buxbaum, Joseph D.; Greengard, Paul
PATENT ASSIGNEE(S): Rockefeller University, USA
SOURCE: U.S., 13 pp., Cont.-in-part of U.S. 5,385,915.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5538983	A	19960723	US 1994-236411	19940429
US 5242932	A	19930907	US 1991-809174	19911217
US 5385915	A	19950131	US 1993-73112	19930607

PRIORITY APPLN. INFO.:
US 1990-524202 19900516
US 1991-809174 19911217
US 1993-73112 19930607

AB Various first messengers linked to phospholipase C, including **acetylcholine** and interleukin-1, regulate the production both of the secreted form of the amyloid protein precursor and of amyloid β-protein. Intracellular signals which are responsible for mediating these effects have now been identified, and that activation of phospholipase C may affect APP processing by either of two pathways, one involving an increase in protein kinase C and the other an increase in cytoplasmic calcium levels. The effects of calcium on APP processing appear to be independent of protein kinase C activation. The observed effects of calcium on APP processing are of therapeutic utility in the treatment of **Alzheimer**-type amyloidosis.

L20 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:341827 CAPLUS
DOCUMENT NUMBER: 125:1414
TITLE: Carbon monoxide-dependent guanylyl cyclase modifiers and their therapeutic use
INVENTOR(S): Glasky, Alvin J.; Rathbone, Michel
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9603125	A1	19960208	WO 1995-US10008	19950725
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5447939	A	19950905	US 1994-280719	19940725
US 5801184	A	19980901	US 1995-488976	19950608
AU 9532775	A1	19960222	AU 1995-32775	19950725
AU 709454	B2	19990826		
EP 772440	A1	19970514	EP 1995-929408	19950725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9508339	A	19970930	BR 1995-8339	19950725
JP 10504814	T2	19980512	JP 1995-506010	19950725
FI 9700302	A	19970124	FI 1997-302	19970124
NO 9700312	A	19970127	NO 1997-312	19970124

PRIORITY APPLN. INFO.:

US 1994-280719	A	19940725
US 1995-488976	A	19950608
US 1995-492929	A	19950720
WO 1995-US10008	W	19950725

AB Methods and associated compns. and medicaments are disclosed which are directed generally to the control of cellular and neural activity and for selectively and controllably inducing the in vivo genetic expression of one or more naturally occurring genetically encoded mols. in mammals. More particularly, the present invention selectively activates or derepresses genes encoding for specific naturally occurring mols., e.g. proteins or neurotrophic factors, and induces the endogenous production of such naturally occurring compds. through the administration of carbon monoxide-dependent guanylyl cyclase modulating purine derivs. The methods of the invention may be used to affect a variety of cellular and neurol. functions and activities and to therapeutically or prophylactically treat a wide variety of neurodegenerative, neurol., cellular, and physiol. disorders. Evaluation of the effects of guanosine, 4-[(3-(1,6-dihydro-6-oxo-9-purin-9-yl)-1-oxopropyl)amino]benzoic acid (AIT-082), and inosine pranobex is included.

L20 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:846894 CAPLUS
DOCUMENT NUMBER: 123:246864
TITLE: Carbon monoxide-dependent guanylyl cyclase modifiers and methods of use for control of neural activity and treatment of neural disorders
INVENTOR(S): Glasky, Alvin J.; Rathbone, Michael P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 40 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5447939	A	19950905	US 1994-280719	19940725
US 5801184	A	19980901	US 1995-488976	19950608

CA 2195302	AA	19960208	CA 1995-2195302	19950725
WO 9603125	A1	19960208	WO 1995-US10008	19950725
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9532775	A1	19960222	AU 1995-32775	19950725
AU 709454	B2	19990826		
EP 772440	A1	19970514	EP 1995-929408	19950725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1154065	A	19970709	CN 1995-194311	19950725
HU 76294	A2	19970728	HU 1996-3591	19950725
BR 9508339	A	19970930	BR 1995-8339	19950725
JP 10504814	T2	19980512	JP 1995-506010	19950725
FI 9700302	A	19970124	FI 1997-302	19970124
NO 9700312	A	19970127	NO 1997-312	19970124
US 6350752	B1	20020226	US 1997-878656	19970619
US 6027936	A	20000222	US 1998-86878	19980529
US 6338963	B1	20020115	US 1999-420543	19991019
US 2002165242	A1	20021107	US 2002-67662	20020204

PRIORITY APPLN. INFO.:

US 1994-280719	A2	19940725
US 1995-488976	A	19950608
US 1995-492929	A	19950720
WO 1995-US10008	W	19950725
US 1997-878656	A1	19970619
US 1998-86878	A2	19980529

AB Methods are disclosed for the control of neural activity and the treatment of neural disorders. More particularly, the invention is directed to methods for the modification of mammalian neural activity through the administration of carbon monoxide-dependent guanylyl cyclase-modulating purine derivs. The methods of the invention may be used to affect a variety of neurol. activities and to therapeutically or prophylactically treat a wide variety of neurodegenerative and neurol. disorders.

L20 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1995:329998 CAPLUS
DOCUMENT NUMBER:	122:95713
TITLE:	Metabolism and actions of CDP-choline as an endogenous compound and administered exogenously as citicoline
AUTHOR(S):	Weiss, George B.
CORPORATE SOURCE:	M. Hurley & Associates, Inc., Murray Hill, NJ, 07947-1584, USA
SOURCE:	Life Sciences (1995), 56(9), 637-60 CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER:	Elsevier
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review with 184 refs. CDP-choline, supplied exogenously as citicoline, has beneficial physiol. actions on cellular function that have been extensively studied and characterized in numerous model systems. As the product of the rate-limiting step in the synthesis of phosphatidylcholine from choline, CDP-choline and its hydrolysis products (cytidine and choline) play important roles in generation of phospholipids involved in membrane formation and repair. They also contribute to such critical metabolic functions as formation of nucleic acids, proteins, and **acetylcholine**. Orally-administered citicoline is hydrolyzed in

the intestine, absorbed rapidly as choline and cytidine, resynthesized in liver and other tissues, and subsequently mobilized in CDP-choline synthetic pathways. Citicoline is efficiently utilized in brain cells for membrane lipid synthesis where it not only increases phospholipid synthesis but also inhibits phospholipid degradation Exogenously administered citicoline prevents, reduces, or reverses effects of ischemia and/or hypoxia in most animal and cellular models studied, and acts in heat trauma models to decrease and limit nerve cell membrane damage, restore intracellular regulatory enzyme sensitivity and function, and limit edema. Thus, considerable accumulated evidence supports use of citicoline to enhance membrane maintenance, membrane repair, and neuronal function in conditions such as ischemic and traumatic injuries. Beneficial effects of exogenous citicoline also have been postulated and/or reported in exptl. models for dyskinesia, Parkinson's disease, aging, **Alzheimer**'s disease, learning and memory, and cholinergic stimulation.

L20 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:548887 CAPLUS
DOCUMENT NUMBER: 121:148887
TITLE: Effects of CDP-choline on cognition and cerebral hemodynamics in patients with **Alzheimer**'s disease
AUTHOR(S): Caamano, J.; Gomez, M.J.; Franco, A.; Cacabelos, R.
CORPORATE SOURCE: Basic Clin. Neurosci. Res. Cent., Inst. C.N.S. Dis., La Coruna, Spain
SOURCE: Methods and Findings in Experimental and Clinical Pharmacology (1994), 16(3), 211-18
CODEN: MFEPDX; ISSN: 0379-0355
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CDP-choline (cytidine-5-diphosphate-choline) is an **acetylcholine** precursor frequently used in cerebrovascular disorders and psychoorg. syndromes. Furthermore, several authors have demonstrated the pos. effects of CDP-choline on cognitive disorders and memory deficits. In the present study, the effects of CDP-choline (1000 mg/day, p.o. for 1 mo) on cognition, evaluated by the Mini-Mental State Examination (MMSE) of Folstein et al., and on blood flow velocities, measured by transcranial Doppler ultrasonog. (TCD), were investigated in patients with **Alzheimer**'s disease: (AD, n = 20, age: 66.75 +/-6.73 yr, range: 57-78 yr). Cognitive function was measured by means of the MMSE in basal conditions (A) and after 1 mo of treatment with CDP-choline (C). TCD measures were taken through the temporal window for right (MCA-R) and left (MCA-L) middle cerebral arteries with a 2 MHz pulsed transducer using a TC-2000S in basal conditions (A), 1 h after the administration of CDP-choline (B) and after 1 mo of treatment with CDP-choline (C). MMSE scores were significantly increased ($p < 0.005$) in patients with early-onset **Alzheimer**'s disease (EOAD) after CDP-choline treatment. Moreover, the orientation subtest significantly increased in the global group of AD patients ($p < 0.01$) and in EOAD patients ($p < 0.02$). Significant differences ($p < 0.05$) were also found in MCA-L and MCA-R measures between recordings. These results suggest that CDP-choline influences cognitive and cerebrovascular function in **Alzheimer**'s disease, probably through a mechanism linked to an immunogenic and/or neurotrophic effect at the microvascular niche. However, a direct vasoactive effect on the vascular endothelium cannot be ruled out.

L20 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:490216 CAPLUS
DOCUMENT NUMBER: 115:90216

TITLE: Changes in pyruvate dehydrogenase complex (PDHc) activity and [3H]QNB-receptor binding in rat brain subsequent to intracerebroventricular injection of bromopyruvate

AUTHOR(S): Froelich, L.; Strauss, M.; Kornhuber, J.; Hoyer, S.; Sorbi, S.; Riederer, P.; Amaducci, L.

CORPORATE SOURCE: Dep. Psychiatry, Univ. Wuerzburg, Wuerzburg, D-8700, Germany

SOURCE: Journal of Neural Transmission: Parkinson's Disease and Dementia Section (1990), 2(3), 169-78
CODEN: JNPSEJ; ISSN: 0936-3076

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pyruvate dehydrogenase complex (PDHc), a link between carbohydrate and **acetylcholine** metabolism, is a regulatory enzyme for glucose and neurotransmitter metabolism in the brain and is reduced in **Alzheimer** -diseased brain. The effects of PDHc inhibition on muscarinic receptor binding were studied using bromopyruvate, a suicide inhibitor od PDHc, injected intracerebroventricularly (i.c.v.) in rats. Bromopyruvate reduced the PDHc activity in the cerebral cortex, hippocampus, and striatum 24 h after injection. At 3, 6, and 12 wk later, there was a normalization or a transient increase of the activity of PDHc in these brain regions. No changes in concns. of energy-rich phosphates could be demonstrated in the cerebral cortex 12 wk after bromopyruvate injection. The number of muscarinic receptors determined by quinuclidinylbenzilate (QNB) binding was reduced in the cerebral cortex 12 wk after injection. A transient reduction of brain PDHc activity in vivo is associated with a long-lasting reduction in muscarinic cholinergic receptors. Because comparable changes in PDHc and muscarinic receptors are found in dementia of **Alzheimer** type, the model of bromopyruvate inhibition of PDHc in rats may be useful for exptl. dementia research.

L20 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1989:470975 CAPLUS

DOCUMENT NUMBER: 111:70975

TITLE: Phosphoethanolamine for treatment of **Alzheimer** 's disease

INVENTOR(S): Appel, Stanley H.

PATENT ASSIGNEE(S): Baylor College of Medicine, USA

SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8809171	A1	19881201	WO 1988-US1693	19880518
W: AU, DK, JP				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
AU 8817909	A1	19881221	AU 1988-17909	19880518

PRIORITY APPLN. INFO.: US 1987-51897 19870519
US 1988-188005 19880511
WO 1988-US1693 19880518

OTHER SOURCE(S): MARPAT 111:70975

AB Stereoisomers of the ethanolamines R1NHCHR2CHR3R4 (R1 = H, alkyl; R2, R3 = H, alkyl, CO2M; R4 = OH, PO3H2, OPO3H2, cytidine-5'-diphosphate or their salts; M = H, cation) are drugs for the treatment of **Alzheimer**'s

disease. Phosphoethanolamine, extracted from the calf brain, stimulated **acetylcholine** biosynthesis, in vitro, with a ED50 value of 5 μM. This finding is important due to the deficiency of **acetylcholine** in **Alzheimer**'s disease.

L20 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:481705 CAPLUS
DOCUMENT NUMBER: 103:81705
TITLE: Therapeutic use of cytidyl diphosphocholine to increase neuronal **acetylcholine**
INVENTOR(S): Growdon, John H.; Wurtman, Richard J.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 147185	A2	19850703	EP 1984-308945	19841220
EP 147185	A3	19870506		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
US 4569929	A	19860211	US 1983-564607	19831222
JP 60252416	A2	19851213	JP 1984-270608	19841221
CA 1248454	A1	19890110	CA 1984-470864	19841221

PRIORITY APPLN. INFO.:

US 1983-564607	19831222
US 1977-847967	19771102
US 1979-88227	19791025
US 1980-126124	19800229
US 1981-229894	19810130
US 1982-366888	19820408

AB Administration of cytidyl diphosphocholine (I) [**987-78-0**] alone increases brain choline levels, thus indirectly raising **acetylcholine** [51-84-3] levels. I administered with an antipsychotic drug potentiates the affect of the drug by increasing the **acetylcholine** levels in the brain or other tissues and/or suppresses or blocks the development of unwanted side effects of the drug. I is also useful in treatment of senility, **Alzheimer**'s disease, tardive diskinesia, Parkinson's disease and other neurol. and behavioral syndromes. I elevated plasma choline levels in rats by 50% after 4 h at 2.25 g/kg. In addition, laboratory rats were given I at 1.5 g/kg or equimolar choline chloride [67-48-1] and killed after 1, 5 and 24 h by focussed microwave irradiation to the head as were controls which were not administered choline chloride or I. Whole brain choline was elevated relative to controls at all times in both I-treated and choline-treated animals. Peak values of choline occurred at 5 h. Choline levels returned near baseline by 24 h. Since administration of I raises brain choline, brain **acetylcholine** levels also are raised.

```
     FILE 'REGISTRY' ENTERED AT 09:09:18 ON 27 FEB 2003
L29             STRUCTURE UPLOADED
L30         35488 L29 SSS FUL
L31             0 L30 AND ACETYLCHOLIN?

     FILE 'REGISTRY' ENTERED AT 09:10:16 ON 27 FEB 2003

     FILE 'CAPLUS' ENTERED AT 09:10:20 ON 27 FEB 2003

=> l30
L32     173792 L30

=> l32 and acetylcholin?
          81231 ACETYLCHOLIN?
L33        1943 L32 AND ACETYLCHOLIN?

=> l33 and alzheimer##
          25098 ALZHEIMER##
L34          21 L33 AND ALZHEIMER##

=> l34 not (l20 or l19 or l28)
L35           0 L34 NOT (L20 OR L19 OR L28)

=> l34 not l20
L36           0 L34 NOT L20

=> l25 and l34
L37           1 L25 AND L34

=> l32 and l25
L38          10 L32 AND L25

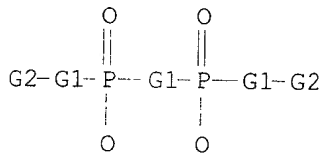
=> l38 not l28
L39           1 L38 NOT L28

=> d l39 ibib abs

L39  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         1994:670307  CAPLUS
DOCUMENT NUMBER:          121:270307
TITLE:                    Synthesis, structure and stability of complexes of
                          lanthanide nitrates with [(MeO)2P(O)]2C(OH)Ph and the
                          isomeric (MeO)2P(O)OCHPhP(O)(OMe)2
AUTHOR(S):                Platt, Andrew W. G.; Simpson, David; Fawcett,
                          John; Russell, David R.
CORPORATE SOURCE:         Chemistry Division, Staffordshire University, College
                          Road, Stoke-on-Trent, ST4 2DE, UK
SOURCE:                   Inorganica Chimica Acta (1994), 223(1-2), 43-53
                          CODEN: ICHAA3; ISSN: 0020-1693
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   The syntheses of compds. Ln(NO3)3L2 (A1-A12) and Ln(NO3)3L'2 (B1-B12),
     where L = [(MeO)2P(O)]2C(OH)Ph and L' = (MeO)2P(O)OCHPhP(O)(OMe)2 and Ln =
     La-Lu except Pm, Tb and Tm, are described.  For the heavier lanthanides
     isomerization of A to B occurs readily in solution  All compds. are prone to
     loss of MeNO3 above ambient temperature, the propensity for this reaction
     increasing with the atomic weight of the metal.  Study by IR and NMR
     spectroscopies indicate that both the series A and B show slight
     differences in structure between the heavier and lighter lanthanides and
     that these differences are probably due to changes in the coordination of
     the nitrate ligands.  The x-ray structures of two isomeric Pr complexes A3
```

(R' = 0.0690 for 5326 diffractometer observed reflections) and B3 (R' = 0.0393 for 4427 diffractometer observed reflections) show that in both cases the metals are ten-coordinated. The H atoms of the OH group in A3 were not located but appear to be H bonded to two of the nitrate groups. One of the ligands in A3 is distorted towards the structure of the isomer. The isomerizations of complexes A to B are discussed in terms of the electrostatic interactions between the P atoms and the metal center.

=> d que l30
L29 STR



G1 O,S,CH2,NH,C,N

G2 C,H,Ak,Cb

Structure attributes must be viewed using STN Express query preparation.
L30 35488 SEA FILE=REGISTRY SSS FUL L29

=> d his l40-

(FILE 'CAPLUS' ENTERED AT 09:10:20 ON 27 FEB 2003)

FILE 'STNGUIDE' ENTERED AT 09:14:15 ON 27 FEB 2003

FILE 'CAPLUS' ENTERED AT 09:15:23 ON 27 FEB 2003
L40 173837 L16 OR L12 OR L32
L41 3608 L40 AND (HEME OR PEROXIDE)
L42 10 L41 AND ACETYLCHOLIN?

=> d l42 total ibib his
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For an explanation, enter "HELP DISPLAY HISTORY".

=> d l42 total ibib abs

L42 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:661750 CAPLUS
DOCUMENT NUMBER: 138:11738
TITLE: Relaxant Effect of Oxygen Free Radicals on Rabbit Tracheal Smooth Muscle
AUTHOR(S): Prasad, Kailash; Gupta, Jang B.
CORPORATE SOURCE: Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, SK, Can.
SOURCE: Pulmonary Pharmacology & Therapeutics (2002), 15(4), 375-384
CODEN: PPTHFJ; ISSN: 1094-5539
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated the effect of exogenously generated superoxide anions (O2-), hydrogen **peroxide** (H2O2) and hydroxyl radicals (•OH) on isolated rabbit tracheal smooth muscle suspended in Krebs-Ringer solution The ability of oxygen free radicals (OFRs) to affect **acetylcholine** (Ach)-induced contraction in these muscles was also investigated. OFRs, in general, produced a concentration-dependent relaxation of the tracheal smooth muscle in the doses used. However, in large concns., O2- and H2O2 produced effects which were smaller than those obtained with lower concns. The relaxant effects of these oxyradicals were progressive and lasted throughout the 20 min observation period. At all concns. used, the OFRs tended to abolish or reduce Ach-induced contraction in a concentration-dependent manner. O2- was more potent than H2O2 or DHF in relaxing the Ach-precontracted muscle and in inhibiting the response of the muscle to Ach. OFR-induced relaxation of the Ach-contracted muscle was not due to inactivation of the Ach by OFRs. Relaxation produced by OFRs was greater in prepns. with intact epithelium than in those denuded of epithelium. The relaxant effects were blocked by indomethacin, a cyclooxygenase inhibitor. OFRs in the presence of indomethacin produced contraction only in the prepns. with intact epithelium, suggesting a release of contractile factor(s) from epithelium. These results suggest that OFRs relax rabbit tracheal smooth muscle. The relaxation appears to be mediated through the synthesis and release of prostaglandins from the epithelium and smooth muscles.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107671 CAPLUS
DOCUMENT NUMBER: 136:163667
TITLE: Methods for biosensor library synthesis and applications of use
INVENTOR(S): Minshull, Jeremy; Davis, S. Christopher; Welch, Mark; Raillard, Sun Ai; Vogel, Kurt; Krebber, Claus
PATENT ASSIGNEE(S): Maxygen, Inc., USA
SOURCE: PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002010750	A2	20020207	WO 2001-US24182	20010731
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002102577	A1	20020801	US 2001-920452	20010731
US 2002127623	A1	20020912	US 2001-920607	20010731

PRIORITY APPLN. INFO.: US 2000-222056P P 20000731
US 2000-244764P P 20001031

AB The invention concerns methods for sensing test stimuli using arrays of biopolymers. Reusable library arrays of biopolymers, such nucleic acid variants, and expression products encoded by nucleic acid variants are provided. The present invention provides novel methods for detecting a wide range of biol., chem. and biochem. stimuli. The methods of the invention utilize biopolymers and arrayed libraries of biopolymers, members of which are capable of binding the biol., chem. or biochem. stimuli, and upon binding produce a detectable signal. Upon contact with the test stimulus, a test stimulus array pattern is produced and detected. The test stimulus array pattern is then compared to the calibrating array pattern enabling identification of the test stimulus. Examples provide extensive listings of suitable hormones and enzymes suitable for such biosensor development. Diagrams describing the apparatus are given.

L42 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:816459 CAPLUS
DOCUMENT NUMBER: 135:339302
TITLE: Methods and compositions for enhancing cellular function through protection of tissue components
INVENTOR(S): Frey, William H., II; Fawcett, John Randall; Thorne, Robert Gary; Chen, Xueqing
PATENT ASSIGNEE(S): Healthpartners Research Foundation, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001082932	A2	20011108	WO 2001-US13931	20010430
WO 2001082932	A3	20020718		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002028786	A1	20020307	US 2001-844450	20010427
EP 1278525	A2	20030129	EP 2001-930957	20010430

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:	US 2000-200843P	P	20000501
	US 2000-230263P	P	20000906
	US 2000-233025P	P	20000915
	US 2000-233263P	P	20000918
	WO 2001-US13931	W	20010430

OTHER SOURCE(S): MARPAT 135:339302

AB Methods and compns. for enhancing cellular function through protection of tissue components, such as receptors, proteins, lipids, nucleic acids, carbohydrates, hormones, vitamins, and cofactors, by administering pyrophosphate analogs or related compds. Preferably, the invention provides a method for protecting a muscarinic **acetylcholine** receptor (mAChR) an/or increasing the efficacy of and agent the directly or indirectly affects a mAChR in a subject in need thereof.

L42 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2001:598653 CAPLUS
DOCUMENT NUMBER:	135:302099
TITLE:	Abnormalities of gallbladder muscle associated with acute inflammation in guinea pigs
AUTHOR(S):	Xiao, Zuo-Liang; Chen, Qian; Biancani, Piero; Behar, Jose
CORPORATE SOURCE:	Department of Medicine, Rhode Island Hospital and Brown University School of Medicine, Providence, RI, 02903, USA
SOURCE:	American Journal of Physiology (2001), 281(2, Pt. 1), G490-G497
	CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER:	American Physiological Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Muscle strips from exptl. acute cholecystitis (AC) exhibit a defective contraction. The mechanisms responsible for this impaired contraction are not known. The present studies investigated the nature of these abnormalities. AC was induced by ligating the common bile duct of guinea pigs for 3 days. Contraction was studied in enzymic dissociated muscle cells. Cholecystokinin (CCK) and prostaglandin E2 (PGE2) receptor binding studies were performed by radioreceptor assay. The levels of lipid peroxidn., cholesterol, phospholipid, and H2O2 as well as the catalase and superoxide dismutase (SOD) activities were determined PGE2 content was measured by RIA. Muscle contraction induced by CCK, ACh, or KCl was significantly reduced in AC, but PGE2-induced contraction remained normal.

GTPγS, diacylglycerol (DAG), and 1,4,5-trisphosphate (IP3), which bypass the plasma membrane, caused a normal contraction in AC. The number of functional receptors for CCK was significantly decreased, whereas those for PGE2 remained unchanged in AC. There was a reduction in the phospholipid content and increase in the level of lipid peroxidn. as well as H2O2 content in the plasma membrane in AC. The PGE2 content and the activities of catalase and SOD were also elevated. These data suggest that AC cause damage to the constituents of the plasma membrane of muscle cells. The preservation of the PGE2 receptors may be the result of muscle cytoprotection.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:338762 CAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
WO 2001032928	A3	20020725		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to determine the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes associated with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes associated with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes associated with hypersensitivity. The expression of the genes predetd. to be associated with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and

apparatus useful for identifying hypersensitivity in a subject are also disclosed.

L42 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:286826 CAPLUS
DOCUMENT NUMBER: 134:348558
TITLE: Significance of endothelial prostacyclin and nitric oxide in peripheral and pulmonary circulation
AUTHOR(S): Gryglewski, Ryszard J.; Chlopicki, Stefan; Uracz, Wojciech; Marcinkiewicz, Ewa
CORPORATE SOURCE: Chair of Pharmacology, Jagiellonian University, Krakow, Pol.
SOURCE: Medical Science Monitor (2001), 7(1), 1-16
CODEN: MSMOFR; ISSN: 1234-1010
PUBLISHER: Medical Science International Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Vasoprotective function of endothelial cells is associated, among others, with biosynthesis and release of nitric oxide (NO), prostacyclin (PGI2), prostaglandin E2 (PGE2), carbon monoxide (CO) and plasminogen activator (t-PA). These endothelial mediators calm down activated platelets and leukocytes, prevent the occurrence of parietal thrombotic events, promote thrombolysis, maintain tissue perfusion and protect vascular wall against acute damage and against chronic remodeling. Endothelial dysfunction in patients suffering from atherosclerosis or diabetes type 2 is associated not only with suppression in release of the above mediators but also with deleterious discharge of prostaglandin endoperoxides (PGH2, PGG2), superoxide anion (O2, peroxynitrite (ONOO-)), and plasminogen activator inhibitor (PAI-1). The authors looked for mechanisms of protective endothelial function, with a special respect to the differences between peripheral and pulmonary circulation. Cultured endothelial cells of bovine aorta (BAEC) were used to study physiol. and pharmacol. mechanisms of increasing free cytoplasmic calcium [Ca2+]i. A porphyrinic sensor quantified the release of NO from BAEC. In cultured human umbilical vein endothelial cells (HUVEC) the authors looked for induction by bradykinin (Bk) of mRNAs for a number of enzymes. In blood perfused rat lungs the authors studied protective role of NO against injury inferred by lipopolysaccharide on pulmonary microcirculation that was accomplished by thromboxane A2 (TXA2), platelet activating factor (PAF), cysteinyl-leukotrienes (cyst-LTs) and the complement system. In vivo the authors analyzed the influence of Bk, perindopril and quinapril ('tissue type' angiotensin converting enzyme inhibitors, ACE-Is) on endothelial function in entire circulation of anesthetized rats using a thrombolytic bioassay and EIA for 6-keto-PGF1α and t-PA antigen. In BAEC Bk via kinin B2 receptors raised in a concentration-dependent manner (1 pM - 10 nM) free cytoplasmic calcium ions [Ca2+]i, that triggered the release of NO from BAEC. Calcium ionophore (A23187, 1-100 nM) as well as receptor agonists such as ADP (ADP, 10 nM - 1 μM), adrenaline (Adr, 1-10 μM) or **acetylcholine** (Ach, 10-100 μM) produced a similar rise in endothelial [Ca2+]i as did Bk at a nanomolar concentration 'Tissue type' ACE-Is, e.g., quinapril or perindopril acted through accumulation of endogenous Bk. However, the potency of ACE-I to change endothelial function is by several orders of magnitude lower than that for exogenous Bk. In vivo the major difference between thrombolytic actions by quinapril or perindopril on one hand, and by exogenous Bk on the other was longevity of thrombolysis by ACE I and a distinct hypotensive action of exogenous Bk. Still, the long-lasting isolated thrombolytic effect of ACE I was mediated

entirely by endogenous Bk as evidenced by the preventive action of icatibant, a kinin B2 receptor antagonist. Moreover, in vivo the immediate thrombolysis by ACE-I was mediated by PGI2 rather than by NO or t-PA, as shown by pharmacol. anal., and by direct blood assays of 6-keto-PGF1α and t-PA antigen. Bradykinin as a mediator of pleiotropic endothelial action of several cardiovascular drugs (e.g., ACE-I) may complete its mission not only through B2 receptor and [Ca2+]i - mediated release of PGI2 or NO. Here, the authors describe a new route of the Bk action. Bk mediated induction of the [Ca2+]i-independent, so called 'inducible', endothelial isoenzymes required for generation of CO, PGI2 and PGE2. After 4 h of incubation of HUVEC with Bk (10 nM) it induced mRNAs for hemo-oxygenase 1 (HO-1), cyclooxygenase 2 (COX-2), prostaglandin E synthase (PGE-S) whereas mRNA for nitric oxide synthase 2 (NOS-2) was weakly affected. The authors proved also that unlike in peripheral circulation, in pulmonary circulation only NO but not PGI2 would play a protective role. In the blood-perfused lung, endotoxemia liberates lipids, such as TXA2, PAF and cyst-LTs. These toxic lipids along with the activated complement mediate pulmonary damage. Pulmonary endothelial nitric oxide is the only local protector against lung injury evoked by the phagocytosed bacterial lipopolysaccharide. Summing up, in peripheral circulation endogenous Bk is the most efficient activator of protective endothelial function. For instance, thrombolytic action of 'tissue type' ACE-I depends on the Bk-released PGI2. Acting as an agonist of endothelial B2 kinin receptors Bk rises [Ca2+]i with a subsequent activation of constitutive COX 1 and NOS-3. This is followed by an immediate release of PGI2 and NO. Moreover, acting as 'microcytokine' Bk induces mRNAs for HO-1, COX-2 and PGE S, the isoenzymes responsible for a delayed endothelial biosynthesis of CO, PGI2 and PGE2. Activation of HO-1, apart from the CO generation may also lead to a deficiency in intracellular **heme** required as a coenzyme for both COX and NOS. In peripheral circulation Bk-triggered production of PGI2 seems to play a major role in defending endothelium against thrombosis. On the contrary, in pulmonary circulation NO seems to be the major endothelial defender against bacterial aggression coming from blood.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:341827 CAPLUS
DOCUMENT NUMBER: 125:1414
TITLE: Carbon monoxide-dependent guanylyl cyclase modifiers and their therapeutic use
INVENTOR(S): Glasky, Alvin J.; Rathbone, Michel
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9603125	A1	19960208	WO 1995-US10008	19950725

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT,

LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 5447939	A	19950905	US 1994-280719	19940725
US 5801184	A	19980901	US 1995-488976	19950608
AU 9532775	A1	19960222	AU 1995-32775	19950725
AU 709454	B2	19990826		
EP 772440	A1	19970514	EP 1995-929408	19950725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9508339	A	19970930	BR 1995-8339	19950725
JP 10504814	T2	19980512	JP 1995-506010	19950725
FI 9700302	A	19970124	FI 1997-302	19970124
NO 9700312	A	19970127	NO 1997-312	19970124

PRIORITY APPLN. INFO.:

US 1994-280719	A	19940725
US 1995-488976	A	19950608
US 1995-492929	A	19950720
WO 1995-US10008	W	19950725

AB Methods and associated compns. and medicaments are disclosed which are directed generally to the control of cellular and neural activity and for selectively and controllably inducing the in vivo genetic expression of one or more naturally occurring genetically encoded mols. in mammals. More particularly, the present invention selectively activates or derepresses genes encoding for specific naturally occurring mols., e.g. proteins or neurotrophic factors, and induces the endogenous production of such naturally occurring compds. through the administration of carbon monoxide-dependent guanylyl cyclase modulating purine derivs. The methods of the invention may be used to affect a variety of cellular and neurol. functions and activities and to therapeutically or prophylactically treat a wide variety of neurodegenerative, neurol., cellular, and physiol. disorders. Evaluation of the effects of guanosine, 4-[(3-(1,6-dihydro-6-oxo-9-purin-9-yl)-1-oxopropyl)amino]benzoic acid (AIT-082), and inosine pranobex is included.

L42 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1995:295747 CAPLUS
DOCUMENT NUMBER:	122:78309
TITLE:	Dopamine or transmitter release from rat carotid body may not be essential to hypoxic chemoreception
AUTHOR(S):	Sun, Miao-Kun; Reis, Donald J.
CORPORATE SOURCE:	Dep. Neurol. Neurosci., Cornell Univ. Med. Coll., New York, NY, 10021, USA
SOURCE:	American Journal of Physiology (1994), 267(6, Pt. 2), R1632-R1639 CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER:	American Physiological Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB In anesthetized, paralyzed, and ventilated rats, hypoxia or intracarotid cyanide excited the carotid chemoafferents, whereas intracarotid dopamine and tyramine inhibited the chemoafferent discharges. The inhibition was abolished by chlorpromazine without attenuating the hypoxic excitation. Comparably, the hypoxic excitation was not attenuated by the following: 1) inhibition of nitric oxide synthase with NG-nitro-L-arginine; 2) inhibition of **heme** oxygenase with zinc protoporphyrin IX; 3) antagonism of ATP receptors with reactive blue 2; 4) antagonism of cholinergic receptors with atropine or trimethaphan; 5) inactivation of adenosine with adenosine deaminase; and 6) blockade of glutamate receptors with kynurenate. Systemic administration of ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid, in doses reversibly blocking sympathetic ganglionic transmission, was also without effect. Cyanide

microinjection (0.05-0.5 nmol) into the petrosal but not nodose ganglion elicited a rapid dose-dependent elevation of arterial pressure. We conclude that excitation of the chemoreceptor afferents by hypoxia/cyanide cannot be attributed to release of these agents nor to others by Ca2+-dependent mechanisms. The results suggest that the afferent nerves themselves might function as oxygen detectors.

L42 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:557376 CAPLUS
DOCUMENT NUMBER: 119:157376
TITLE: Hypercholesterolemia promotes endothelial dysfunction in vitamin E- and selenium-deficient rats
AUTHOR(S): Raij, Leopoldo; Nagy, Judit; Coffee, Karen; DeMaster, Eugene G.
CORPORATE SOURCE: Med. Res. Serv., Veterans Aff. Med. Cent., Minneapolis, MN, 55417, USA
SOURCE: Hypertension (1993), 22(1), 56-61
CODEN: HPRTDN; ISSN: 0194-911X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Abnormal regulation of local vascular tone occurs early in human and exptl. atherosclerosis. Impaired endothelium-dependent vascular relaxation mediated by endothelium-derived relaxing factor (EDRF) are an important contributor to these abnormalities. EDRF is nitric oxide released as such or attached to a carrier mol. Oxidized lipoproteins impede EDRF-mediated responses in vitro. The authors designed in vivo expts. to determine whether hypercholesterolemia with and without deficiency of 2 endogenous lipid antioxidants, vitamin E and Se, would result in endothelial dysfunction. Vitamin E and Se deficiencies were induced in a group of hypertension-prone Dahl salt-sensitive rats fed a diet high in cholesterol (4%) but low in NaCl (0.5%) for 18 wk. Two other groups of Dahl salt-sensitive rats received diets sufficient in vitamin E and Se, but containing either high or normal cholesterol levels (control group). Serum cholesterol levels increased .apprx.10-fold in the 2 groups of rats fed high-cholesterol diets. Systolic blood pressure was 143 mm Hg in high-cholesterol/vitamin E- and Se-sufficient rats and 142 mm Hg in high-cholesterol/vitamin E- and Se-deficient rats. Mild intimal thickening and occasional mononuclear cell infiltration were observed in both of these groups. Serum vitamin E levels were decreased, whereas serum thiobarbituric acid-reactive substances and exhaled pentane (indicators of endogenous lipid oxidation) were significantly increased in high-cholesterol/vitamin E- and Se-deficient rats compared with high-cholesterol/vitamin E- and Se-sufficient rats. Vascular relaxation to **acetylcholine** and ADP, agonists of endothelium-dependent relaxation, were significantly impaired in aortic rings from only the high-cholesterol/vitamin E- and Se-deficient rats. Neither indomethacin nor the scavenger of superoxide anion, superoxide dismutase, normalized relaxations in the impaired aortic rings. Relaxations in response to the endothelium-independent vasodilator sodium nitroprusside were normal in all 3 rat groups. Apparently, hypercholesterolemia coexisting with increased levels of endogenous oxidants or deficient levels of antioxidants results in impaired endothelium-dependent vasodilation mediated by EDRF.

L42 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:95836 CAPLUS
DOCUMENT NUMBER: 118:95836
TITLE: Mechanism of hydrogen **peroxide**-induced modulation of airway smooth muscle

AUTHOR(S): Gupta, Jang B.; Prasad, Kailash
CORPORATE SOURCE: Coll. Med., Univ. Saskatchewan, Saskatoon, SK, S7N 0W0, Can.
SOURCE: American Journal of Physiology (1992), 263(6, Pt. 1), L714-L722
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated the effects of H2O2 generated by glucose (G) and glucose oxidase (GO) on the isolated rabbit tracheal smooth muscle suspended in Krebs-Ringer solution H2O2 generated by G + GO was measured with luminol-dependent chemiluminescence. G + GO in the concns. of 1 + (1.80 μM G, 0.075 U/mL GO) and 2, 4, and 8x generated 1.35, 3.2, 6.10, and 6.00 μM of H2O2, resp. H2O2 produced relaxation of rabbit tracheal smooth muscle, relaxed **acetylcholine** (ACh)-precontracted muscle, and reduced muscle responsiveness to ACh. These effects were concentration dependent. H2O2, however, produced contraction of guinea pig tracheal smooth muscle. Catalase completely inhibited the H2O2-induced relaxation of ACh-precontracted tracheal smooth muscle. H2O2-induced relaxation was greater in prepns. with intact epithelium (65%) than in those denuded of epithelium (40%). The relaxant effects of H2O2 in the presence of an inhibitor of guanylate cyclase (methylene blue), an inhibitor of cyclooxygenase (indomethacin), and an ATP-sensitive K+ channel blocker (glipizide) were 44, 44, 39, and 48%, resp. H2O2-induced relaxation in the presence of indomethacin in prepns. with denuded epithelium was 29%. These results suggest that H2O2-induced relaxation of tracheal smooth muscle is partly epithelium dependent and is mediated by inhibitory arachidonic acid metabolites, epithelium-derived relaxing factor (nitric oxide), ATP-sensitive K+ channels, and the synthesis and release of prostaglandins from epithelium and the underlying smooth muscle.

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=> 148 and (toxic? or poison?)
        437093 TOXIC?
         79136 POISON?
L50          6 L48 AND (TOXIC? OR POISON?)

=> d l50 total ibib abs

L50  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2001:816459  CAPLUS
DOCUMENT NUMBER:         135:339302
TITLE:                   Methods and compositions for enhancing cellular
                         function through protection of tissue components
INVENTOR(S):             Frey, William H., II; Fawcett, John Randall; Thorne,
                         Robert Gary; Chen, Xueqing
PATENT ASSIGNEE(S):      Healthpartners Research Foundation, USA
SOURCE:                  PCT Int. Appl., 77 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     WO 2001082932      A2   20011108       WO 2001-US13931   20010430
     WO 2001082932      A3   20020718
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
             ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     US 2002028786      A1   20020307       US 2001-844450    20010427
     EP 1278525         A2   20030129       EP 2001-930957    20010430
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.:                    US 2000-200843P  P  20000501
                                          US 2000-230263P  P  20000906
                                          US 2000-233025P  P  20000915
                                          US 2000-233263P  P  20000918
                                          WO 2001-US13931  W  20010430
OTHER SOURCE(S):         MARPAT 135:339302
AB   Methods and compns. for enhancing cellular function through protection of
     tissue components, such as receptors, proteins, lipids, nucleic acids,
     carbohydrates, hormones, vitamins, and cofactors, by administering
     pyrophosphate analogs or related compds.  Preferably, the invention
     provides a method for protecting a muscarinic acetylcholine receptor
     (mAChR) an/or increasing the efficacy of and agent the directly or
     indirectly affects a mAChR in a subject in need thereof.

L50  ANSWER 2 OF 6  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2000:132182  CAPLUS
DOCUMENT NUMBER:         132:156254
TITLE:                   Estimating the environmental behavior of inorganic and
                         organometal contaminants: solubilities,
                         bioaccumulation, and acute aquatic toxicities
```

AUTHOR(S): Hickey, James P.
CORPORATE SOURCE: U.S. Geological Survey, Ann Arbor, MI, USA
SOURCE: Water-Resources Investigations Report (United States Geological Survey) (1999), 99-4018B, U.S. Geological Survey Toxic Substances Hydrology Program, 1999, Vol. 2, 477-482
CODEN: WIREFS
DOCUMENT TYPE: Report
LANGUAGE: English

AB Estimating environmental properties of inorg. species has been difficult. Aqueous solubility, bio-concentration, and acute aquatic **toxicity** were evaporating for inorg. compds. using existing Linear Solvation Energy Relationship (LSER) equations. Many estns. fell within 1 order of magnitude of the measured property. For complex solution chem., estimation accuracy improved with a more complete description of the solution species present. **Toxicity** also depended on an evaporating bioactive amount and configuration. A number of anion/cation combinations (salts) still resist accurate property estimation; the reasons are not yet understood. These new variable values will greatly extend the application and utility of LSER for estimating environmental properties.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:83178 CAPLUS
DOCUMENT NUMBER: 112:83178
TITLE: Reportable quantity adjustments; delisting of ammonium thiosulfate
CORPORATE SOURCE: United States Environmental Protection Agency, Washington, DC, 20460, USA
SOURCE: Federal Register (1989), 54(155), 33426-84, 14 Aug 1989
CODEN: FEREAC; ISSN: 0097-6326
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Under the Federal Comprehensive Environmental Response, Compensation, and Liability Act, the EPA is promulgating final reportable quantities (RQ) for 258 hazardous substances and hazardous waste streams. NH4 thiosulfate is removed from the list of hazardous substances since the median lethal concentration is well above 500 mg/L for aquatic **toxicity**. Also included in this final rule is replacement of the registered trademark Gelthane with the generic name difocal, as several companies manufacture this substance.

L50 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:401655 CAPLUS
DOCUMENT NUMBER: 103:1655
TITLE: Acute oral **toxicity** and repellency of 933 chemicals to house and deer mice
AUTHOR(S): Schafer, E. W., Jr.; Bowles, W. A., Jr.
CORPORATE SOURCE: Denver Wildl. Res. Cent., Fish Wildl. Serv., Denver, CO, 80225, USA
SOURCE: Archives of Environmental Contamination and Toxicology (1985), 14(1), 111-29
CODEN: AECTCV; ISSN: 0090-4341
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Five individual bioassay repellency or **toxicity** variables were evaporating or determined for deer mice (Peromyscus maniculatus) and house mice (Mus musculus) under laboratory conditions. ALD's (Approx. LDs) or LD50's of 230 chems. to deer mice are presented, as are food reduction (FR) values (3-day feeding test as a 2.0% treatment rate) for white wheat seeds (Triticum aestivum) for 696 chems. and for Douglas fir seeds (Pseudotsuga menziesii) for 81 chems. A similar repellency evaluation (REP) using a 5-day test with white wheat seeds at a 2.0% treatment rate was conducted with house mice and the results for 347 chems. are presented. These **toxicity** and repellency data should be useful to those desiring to predict the potential for acute **toxicity** in wild mammals following exposure to a wide variety of chems. A calcn. of the daily chem. dose ingested in mg/kg/day during the wheat test on deer mice and its resultant effects on mortality are also presented for most of the 696 chems. This calculated value, when used along with the ALD or LD50, should permit a rough estimate of the potential subacute **toxicity** of any tested chem. on wild mammals for which both types of data are available.

L50 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1980:632013 CAPLUS
DOCUMENT NUMBER: 93:232013
TITLE: **Toxicity** of organo-lead compounds, study of bacteria inactivity by ATP measurement
AUTHOR(S): Charlou, J. L.; Martin, G.; Chaussepied, M.; Houeix, A.
CORPORATE SOURCE: Brest, Fr.
SOURCE: Progress in Water Technology (1980), 12(4), 501-12
CODEN: PGWTA2; ISSN: 0306-6746
DOCUMENT TYPE: Journal
LANGUAGE: French
AB The **toxicity** of Et4Pb [78-00-2] and its degradation products, Et3PbCl [1067-14-7], Et2PbCl2 [13231-90-8], and PbCl2 to denitrification heterotrophic microorganisms existing in estuarine and marine sediment was evaluated by measuring ATP [**56-65-5**] levels. Generally, the **toxicity** followed this order: Et3Pb+ > Et2Pb2+ > Pb2+. Additives such as C2H4Cl2 and C2H4Br2 increased the **toxicity** of Et4Pb. A linear correlation existed between the reduction of ATP and the decline of the denitrification rate after addition of the organolead compds.

L50 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1977:561479 CAPLUS
DOCUMENT NUMBER: 87:161479
TITLE: Inhibition of urease by miscellaneous ions and compounds. Implications for the therapy of infection-induced urolithiasis
AUTHOR(S): Burr, R. G.
CORPORATE SOURCE: Natl. Spinal Injuries Cent., Stoke Mandeville Hosp., Aylesbury, UK
SOURCE: Investigative Urology (1977), 15(2), 180-2
CODEN: INURAQ; ISSN: 0021-0005
DOCUMENT TYPE: Journal
LANGUAGE: English
AB One hundred forty-eight drugs and other organic and inorg. substances were screened for their ability to inhibit the enzyme urease [9002-13-5] in an in vitro system modeled on infected urine. The reported urease-inhibiting properties of ascorbic acid, tetracyclines, and sulfanilamide were not confirmed. At least 50 % inhibition was observed in the presence of kanamycin [8063-07-8], hydroxyguanidine [13115-21-4], benzoquinone

[106-51-4], 1,2-naphthoquinone-4-sulfonate [2066-93-5], chloramine-T [127-65-1] N-bromoacetamide [79-15-2], Cu, Hg, and F. It is, however, unlikely that therapeutically effective concns. can be attained in urine without giving dosages likely to result in **toxic** effects. Hydroxyurea [127-07-1], at the dose level used in cytotoxic therapy, may be expected to produce effective inhibition of bacterial urease in the urinary tract, providing renal function is unimpaired and providing urinary volume does not exceed 1 L/24 h. Acetohydroxamic acid [546-88-3] is potentially the most useful drug for the treatment of infection-induced urinary stone disease available at present.

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=> l40 and (oxidative(w)stress)
        157710 OXIDATIVE
            20 OXIDATIVES
        157713 OXIDATIVE
                  (OXIDATIVE OR OXIDATIVES)
        382263 STRESS
         77057 STRESSES
        414749 STRESS
                  (STRESS OR STRESSES)
         26931 OXIDATIVE(W)STRESS
L51        907 L40 AND (OXIDATIVE(W)STRESS)

=> l51 and acetylcholin?
         81231 ACETYLCHOLIN?
L52         11 L51 AND ACETYLCHOLIN?

=> d l52 total ibib abs

L52  ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:661750  CAPLUS
DOCUMENT NUMBER:          138:11738
TITLE:                    Relaxant Effect of Oxygen Free Radicals on Rabbit
                          Tracheal Smooth Muscle
AUTHOR(S):                Prasad, Kailash; Gupta, Jang B.
CORPORATE SOURCE:         Department of Physiology, College of Medicine,
                          University of Saskatchewan, Saskatoon, SK, Can.
SOURCE:                   Pulmonary Pharmacology & Therapeutics (2002), 15(4),
                          375-384
                          CODEN: PPTHFJ; ISSN: 1094-5539
PUBLISHER:                Elsevier Science Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   We investigated the effect of exogenously generated superoxide anions
     (O2-), hydrogen peroxide (H2O2) and hydroxyl radicals (•OH) on
     isolated rabbit tracheal smooth muscle suspended in Krebs-Ringer solution
     The ability of oxygen free radicals (OFRs) to affect acetylcholine
     (Ach)-induced contraction in these muscles was also investigated.  OFRs,
     in general, produced a concentration-dependent relaxation of the tracheal
smooth
     muscle in the doses used.  However, in large concns., O2- and H2O2
     produced effects which were smaller than those obtained with lower concns.
     The relaxant effects of these oxyradicals were progressive and lasted
     throughout the 20 min observation period.  At all concns. used, the OFRs
     tended to abolish or reduce Ach-induced contraction in a
concentration-dependent
     manner.  O2- was more potent than H2O2 or DHF in relaxing the
     Ach-precontracted muscle and in inhibiting the response of the muscle to
     Ach.  OFR-induced relaxation of the Ach-contracted muscle was not due to
     inactivation of the Ach by OFRs.  Relaxation produced by OFRs was greater
     in prepns. with intact epithelium than in those denuded of epithelium.
     The relaxant effects were blocked by indomethacin, a cyclooxygenase
     inhibitor.  OFRs in the presence of indomethacin produced contraction only
     in the prepns. with intact epithelium, suggesting a release of contractile
     factor(s) from epithelium.  These results suggest that OFRs relax rabbit
     tracheal smooth muscle.  The relaxation appears to be mediated through the
     synthesis and release of prostaglandins from the epithelium and smooth
     muscles.
REFERENCE COUNT:          52    THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L52 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:437798 CAPLUS
DOCUMENT NUMBER: 137:261077
TITLE: Mineralocorticoid receptor antagonism in experimental atherosclerosis
AUTHOR(S): Rajagopalan, Sanjay; Duquaine, Damon; King, Steven; Pitt, Bertram; Patel, Paresh
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA
SOURCE: Circulation (2002), 105(18), 2212-2216
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aldosterone has been implicated in the effects of angiotensin II in the vasculature. We hypothesized that there is local expression of the mineralocorticoid receptor (MR) in the vasculature and that the use of a selective aldosterone receptor antagonist (SARA) improves endothelial function in early atherosclerosis. New Zealand rabbits were placed on normal chow or 1% cholesterol diets, randomized to placebo or SARA (eplerenone, 50 mg/kg twice daily), and killed at the end of 6 wk for various studies. In the hyperlipidemic (HL) chow group, there was a 2.3-fold increase in superoxide (O2.-) generation. SARA normalized O2.- generation in intact aortas and reduced NADH and NADPH oxidase activity to basal levels (0.31±0.04 and 0.27±0.02 in HL vs. 0.16±0.05 and 0.07±0.02 in HL-SARA, resp.; P<0.01 by ANOVA). This was associated with improvements in peak relaxations to the endothelial-dependent agonist **acetylcholine** (82±6% in HL-SARA vs. 61±4 in HL; P<0.01 by ANOVA; ED50 6.8 + 10-8 mol/L in HL-SARA and 1.2 + 10-7 mol/L in HL; P=NS) to near-normal levels. Vessels from the HL group demonstrated hyperreactivity to angiotensin II that could not be corrected with SARA. Plasma aldosterone levels by RIA demonstrated a 4- to 5-fold increase in response to SARA but no differences with lipid feeding. Real-time reverse transcriptase-polymerase chain reaction studies revealed expression of MR in the aorta of HL rabbits and those of controls. MR antagonism improves endothelial function and reduces O2.- generation in diet-induced atherosclerosis. Targeting aldosterone by blocking its receptor has potential antiatherosclerotic effects.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L52 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:290493 CAPLUS
DOCUMENT NUMBER: 137:30871
TITLE: Endothelial dysfunction in aging animals: the role of poly(ADP-ribose) polymerase activation
AUTHOR(S): Pacher, Pal; Mabley, Jon G.; Soriano, Francisco G.; Liaudet, Lucas; Komjati, Katalin; Szabo, Csaba
CORPORATE SOURCE: Inotek Corporation, Beverly, MA, 01915, USA
SOURCE: British Journal of Pharmacology (2002), 135(6), 1347-1350
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent work has demonstrated the production of reactive oxygen and nitrogen species in the vasculature of aging animals. Oxidant induced cell injury triggers the activation of nuclear enzyme poly(ADP ribose) polymerase

(PARP) leading to endothelial dysfunction in various pathophysiol. conditions (reperfusion, shock, diabetes). Here we studied whether the loss of endothelial function in aging rats is dependent upon the PARP pathway within the vasculature. Young (3 mo-old) and aging (22 mo-old) Wistar rats were treated for 2 mo with vehicle or the PARP inhibitor PJ34. In the vehicle-treated aging animals there was a significant loss of endothelial function, as measured by the relaxant responsiveness of vascular rings to **acetylcholine**. Treatment with PJ34, a potent PARP inhibitor, restored normal endothelial function. There was no impairment of the contractile function and endothelium-independent vasodilatation in aging rats. Furthermore, we found no deterioration in the myocardial contractile function in aging animals. Thus, intraendothelial PARP activation may contribute to endothelial dysfunction associated with aging.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L52 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:88342 CAPLUS
DOCUMENT NUMBER: 137:3556
TITLE: Tissue-specific expression of human lipoprotein lipase in the vascular system affects vascular reactivity in transgenic mice
AUTHOR(S): Esenabhalu, Victor E.; Cerimagic, Mirza; Malli, Roland; Osibow, Karin; Levak-Frank, Sanja; Frieden, Maud; Sattler, Wolfgang; Kostner, Gerhard M.; Zechner, Rudolf; Graier, Wolfgang F.
CORPORATE SOURCE: Department of Medical Biochemistry and Medical Molecular Biology, Karl-Franzens University of Graz, Graz, A-8010, Austria
SOURCE: British Journal of Pharmacology (2002), 135(1), 143-154
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role of smooth muscle-derived lipoprotein lipase (LPL) that translocates to the endothelium surface on vascular dysfunction during atherogenesis is unclear. Thus, the role of vascular LPL on blood vessel reactivity was assessed in transgenic mice that specifically express human LPL in the circulatory system. Aortic free fatty acids (FFAs) were increased by 69% in the transgenic mice expressing human LPL in aortic smooth muscle cells (L2LPL) compared with their non-transgenic littermates (L2). Contractility to KCl was increased by 33% in aortae of L2LPL mice. Maximal contraction to phenylephrine (PE) was comparable in L2 and L2LPL animals, while the frequency of tonus oscillation to PE increased by 104% in L2LPL mice. In L2LPL animals, .NO mediated relaxation to **acetylcholine** (ACh) and ATP was reduced by 47 and 32%, resp. In contrast, endothelium-independent relaxation to sodium nitroprusside (SNP) was not different in both groups tested. ATP-initiated Ca2+ elevation that triggers .NO formation was increased by 41% in single aortic endothelial cells freshly isolated from L2LPL animals. In aortae from L2LPL mice an increased .O2- release occurred that was normalized by removing the endothelium and by the NAD(P)H oxidase inhibitor DPI and the PKC inhibitor GF109203X. The reduced ACh-induced relaxation in L2LPL animals was normalized in the presence of SOD, indicating that the reduced relaxation is due, at least in part, to enhanced .NO scavenging by .O2-. These data suggest that despite normal lipoprotein levels increased LPL-mediated FFAs loading initiates vascular dysfunction via PKC-mediated

activation of endothelial NAD(P)H oxidase. Thus, vascular LPL activity might represent a primary risk factor for atherosclerosis independently from cholesterol/LDL levels.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L52 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:41422 CAPLUS
DOCUMENT NUMBER: 136:245005
TITLE: Coordinate regulation of L-arginine uptake and nitric oxide synthase activity in cultured endothelial cells
AUTHOR(S): Hardy, Thomas A.; May, James M.
CORPORATE SOURCE: Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA
SOURCE: Free Radical Biology & Medicine (2002), 32(2), 122-131
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Despite intracellular L-arginine concns. that should saturate endothelial nitric oxide synthase (eNOS), nitric oxide production depends on extracellular L-arginine. The authors addressed this 'arginine paradox' in bovine aortic endothelial cells by simultaneously comparing the substrate dependence of L-arginine uptake and intracellular eNOS activity, the latter measured as L-[3H]arginine conversion to L-[3H]citrulline. Whereas the Km of eNOS for L-arginine was 2 μM in cell exts., the L-arginine concentration of half-maximal eNOS stimulation was increased to 29 μM in intact cells. This increase likely reflects limitation by L-arginine uptake, which had a Km of 108 μM. The effects of inhibitors of endothelial nitric oxide synthesis also suggested that extracellular L-arginine availability limits intracellular eNOS activity. Treatment of intact cells with the calcium ionophore A23187 reduced the L-arginine concentration of half-maximal eNOS activity, which is consistent with a measured increase in L-arginine uptake. Increases in eNOS activity induced by several agents were closely correlated with enhanced L-arginine uptake into cells (r = 0.89). The 'arginine paradox' may be explained in part by regulated L-arginine uptake into a compartment, probably represented by caveolae, that contains eNOS and that is distinct from the bulk cytosolic L-arginine.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L52 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:816459 CAPLUS
DOCUMENT NUMBER: 135:339302
TITLE: Methods and compositions for enhancing cellular function through protection of tissue components
INVENTOR(S): Frey, William H., II; Fawcett, John Randall; Thorne, Robert Gary; Chen, Xueqing
PATENT ASSIGNEE(S): Healthpartners Research Foundation, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001082932	A2	20011108	WO 2001-US13931	20010430
WO 2001082932	A3	20020718		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002028786	A1	20020307	US 2001-844450	20010427
EP 1278525	A2	20030129	EP 2001-930957	20010430

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:	US 2000-200843P	P	20000501
	US 2000-230263P	P	20000906
	US 2000-233025P	P	20000915
	US 2000-233263P	P	20000918
	WO 2001-US13931	W	20010430

OTHER SOURCE(S): MARPAT 135:339302

AB Methods and compns. for enhancing cellular function through protection of tissue components, such as receptors, proteins, lipids, nucleic acids, carbohydrates, hormones, vitamins, and cofactors, by administering pyrophosphate analogs or related compds. Preferably, the invention provides a method for protecting a muscarinic **acetylcholine** receptor (mAChR) an/or increasing the efficacy of and agent the directly or indirectly affects a mAChR in a subject in need thereof.

L52 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2001:584332 CAPLUS
DOCUMENT NUMBER:	135:268557
TITLE:	Nitric oxide modulates high-energy phosphates in brain regions of rats intoxicated with diisopropylphosphorofluoridate or carbofuran: prevention by N-tert-butyl-α-phenylnitrone or vitamin E
AUTHOR(S):	Gupta, Ramesh C.; Milatovic, Dejan; Dettbarn, Wolf D.
CORPORATE SOURCE:	Toxicology Department, Murray State University, Breathitt Veterinary Center, Hopkinsville, KY, 42241-2000, USA
SOURCE:	Archives of Toxicology (2001), 75(6), 346-356 CODEN: ARTODN; ISSN: 0340-5761
PUBLISHER:	Springer-Verlag
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Acute effects of seizure-inducing doses of the organophosphate compound diisopropylphosphorofluoridate (DFP, 1.25 mg/kg s.c.) or the carbamate insecticide carbofuran (CF, 1.25 mg/kg s.c.) on nitric oxide (NO) were studied in the brain of rats. Brain regions (pyriform cortex, amygdala, and hippocampus) were assayed for citrulline as the determinant of NO and for high-energy phosphates (ATP and phosphocreatine) as well as their major metabolites (ADP, AMP, and creatine). Rats, anesthetized with sodium pentobarbital (50 mg/kg i.p.), were killed using a head-focused microwave (power, 10 kW; duration, 1.7 s). Analyses of brain regions of controls revealed significantly higher levels of citrulline in the amygdala (289.8±7.0 nmol/g), followed by the hippocampus (253.8±5.5 nmol/g), and cortex (121.7±4.3 nmol/g). Levels of energy metabolites

were significantly higher in cortex than in amygdala or hippocampus. Within 5 min of CF injection, the citrulline levels were markedly elevated in all three brain regions examined, while with DFP treatment, only the cortex levels were elevated at this time. With either **acetylcholinesterase** (AChE) inhibitor, the maximum increase in citrulline levels was noted 30 min post-injection (>6- to 7-fold in the cortex, and >3- to 4-fold in the amygdala or hippocampus). Within 1 h following DFP or CF injection, marked declines in ATP (36-60%) and phosphocreatine (28-53%) were seen. Total adenine nucleotides and total creatine compds. were reduced (36-58% and 28-48%, resp.). The inverse relationship between the increase in NO and the decease in high-energy phosphates, could partly be due to NO-induced impaired mitochondrial respiration leading to depletion of energy metabolites. Pretreatment of rats with an antioxidant, the spin trapping agent N-tert-butyl-α-phenylnitrone (PBN, 200 mg/kg i.p.), prevented DFP- or CF-induced seizures, while the antioxidant vitamin E (100 mg/kg i.p. per day for 3 days) had no anticonvulsant effect. Both antioxidants, however, significantly prevented the increase of citrulline and the depletion of high-energy phosphates. It is concluded that seizures induced by DFP and CF produce **oxidative stress** due to a marked increase in NO, causing mitochondrial dysfunction, and thereby depleting neuronal energy metabolites. PBN pretreatment provides protection against AChE inhibitor-induced **oxidative stress** mainly by preventing seizures. Addnl. antioxidant actions of PBN may contribute to its protective effects. Vitamin E has direct antioxidant effects by preventing excessive NO production

REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L52 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:474613 CAPLUS
DOCUMENT NUMBER: 136:210422
TITLE: Depletion of energy metabolites following **acetylcholinesterase** inhibitor-induced status epilepticus: protection by antioxidants
AUTHOR(S): Gupta, Ramesh C.; Milatovic, Dejan; Dettbarn, Wolf-D.
CORPORATE SOURCE: Toxicology Department, Breathitt Veterinary Center, Murray State University, Hopkinsville, KY, USA
SOURCE: Neurotoxicology (2001), 22(2), 271-282
CODEN: NRTXDN; ISSN: 0161-813X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Status epilepticus (SE)-induced neuronal injury may involve excitotoxicity, energy impairment and increased generation of reactive oxygen species (ROS). Potential treatment therefore should consider agents that protect mitochondrial function and ROS scavengers. In the present study, we examined whether the spin trapping agent N-tert-butyl-α-phenylnitrone (PBN) and the antioxidant vitamin E (α-tocopherol) protect levels of high-energy phosphates during SE. In rats, SE was induced by either of two inhibitors of **acetylcholinesterase** (AChE), the organophosphate diisopropylphosphorofluoridate (DFP, 1.25 mg/kg, s.c.)- or the carbamate carbofuran (1.25 mg/kg, s.c.). Rats were sacrificed 1 h or 3 days after onset of seizures by head-focused microwave (power, 10 kW; duration 1.7 s) and levels of the energy-rich phosphates, ATP, phosphocreatine (PCr) and their metabolites ADP and AMP, and creatine (Cr), resp., were determined in the cortex, amygdala and hippocampus. Within 1 h of seizure activity, marked declines were seen in ATP (34-60%) and PCr (25-52%). Total adenine

nucleotides (TAN = ATP + ADP + AMP) and total creatine compds. (TCC = PCr + Cr) were also reduced (TAN 38-60% and TCC 25-47%). No changes in ATP/AMP ratio were seen. Three days after the onset of seizures, recovery of ATP and PCr was significant in the amygdala and hippocampus, but not in the cortex. Pretreatment of rats with PBN (200 mg/kg, i.p., in a single dose), 30 min before DFP or carbofuran administration, prevented induced seizures and partially prevented depletion of high-energy phosphates. Pretreatment with the natural antioxidant vitamin E (100 mg/kg, i.p./day for 3 days), partially prevented loss of high-energy phosphates without affecting seizures. In controls, citrulline, a product of nitric oxide synthesis, was found to be highest in the amygdala, followed by hippocampus, and lowest in the cortex. DFP- or carbofuran-induced seizures caused elevation of citrulline levels seven- to eight-fold in the cortex and three- to four-fold in the amygdala and hippocampus. These results suggest a close relationship between SE, excitotoxicity and energy metabolism The involvement of **oxidative stress** is supported by the findings that DFP and carbofuran trigger an excessive nitric oxide (NO) production in the seizure relevant regions of the brain.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L52 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:309342 CAPLUS

DOCUMENT NUMBER: 135:15371

TITLE: Temporal effect of alcohol consumption on reactivity of pial arterioles: role of oxygen radicals

AUTHOR(S): Sun, Hong; Mayhan, William G.

CORPORATE SOURCE: Department of Physiology and Biophysics, University of Nebraska Medical Center, Omaha, NE, 68198, USA

SOURCE: American Journal of Physiology (2001), 280(3, Pt. 2), H992-H1001
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Chronic alc. consumption reduces nitric oxide synthase-dependent responses of pial arterioles via mechanisms that remain uncertain. In addition, the temporal effects of alc. on pial arterioles is unclear. Thus the authors' goals were to examine the role of oxygen-derived free radicals in alc.-induced impairment of cerebrovascular reactivity and the temporal effect of alc. on reactivity of pial arterioles. Sprague-Dawley rats were pair-fed a liquid diet with or without alc. for 2-3 wk, 2-3 mo, or 5-6 mo. The authors measured the in vivo diameter of pial arterioles in response to nitric oxide synthase-dependent dilators **acetylcholine** and ADP and the nitric oxide synthase-independent dilator nitroglycerin. In nonalc.-fed rats, **acetylcholine** (1.0 and 10 μM) and ADP (10 and 100 μM) produced dose-related dilatation of pial arterioles. Whereas there was no difference in reactivity of arterioles to the agonists in rats fed the nonalc. and alc. diets for a period of 2-3 wk, there was a significant impairment in reactivity of arterioles to **acetylcholine** and ADP, but not nitroglycerin, in rats fed the alc. diet for longer durations. The authors then found that treatment with superoxide dismutase did not alter baseline diameter of pial arterioles in nonalc.-fed or alc.-fed rats, but significantly improved impaired nitric oxide synthase-dependent dilatation of pial arterioles in alc.-fed rats. Thus these findings suggest a temporal relationship in the effects of alc. on reactivity of pial arterioles and that impaired nitric oxide synthase-dependent cerebral vasodilatation during chronic alc. consumption may be related, in part, to enhanced release of oxygen-derived free

radicals.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L52 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:309113 CAPLUS
DOCUMENT NUMBER: 133:100727
TITLE: In vitro and in vivo effects of chlorpyrifos on glutathione peroxidase and catalase in developing rat brain
AUTHOR(S): Jett, David A.; Navoa, Ryman V.
CORPORATE SOURCE: Department of Environmental Health Sciences, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD, 21205, USA
SOURCE: Neurotoxicology (2000), 21(1 & 2), 141-145
CODEN: NRTXDN; ISSN: 0161-813X
PUBLISHER: Intox Press, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Preliminary findings of a study on the role of **oxidative stress** in the developmental neurotoxicity of chlorpyrifos (CPF) indicates that in vitro exposure to 1-100 μM CPF or 1-100 nM CPF-oxon had no effect on the activity of glutathione peroxidase (GSHpx) in brain homogenates from postnatal day (PN) 21 rats, or on the activity of purified GSHpx. A single high-dose acute injection of 45 mg/kg CPF to PN19 rats also did not significantly alter GSHpx activity at PN21, in spite of extensive (72%) brain **acetylcholinesterase** (AChE) inhibition. However, catalase activity was significantly reduced by 28%. PN21 pups exposed maternally to a lower ED of CPF throughout development (dams injected with 50 mg/kg every 3 days) also had normal GSHpx activity, but a 30% increase in H2O2-independent NADPH consumption. Brain catalase activity in these rats was significantly increased by 24%. These preliminary data suggest that specific GSHpx activity is not altered by in vitro or in vivo exposures to CPF-oxon or CPF, but catalase and an unknown H2O2-independent NADPH-consuming factor were affected differentially depending on the type and timing of exposure.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L52 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:341827 CAPLUS
DOCUMENT NUMBER: 125:1414
TITLE: Carbon monoxide-dependent guanylyl cyclase modifiers and their therapeutic use
INVENTOR(S): Glasky, Alvin J.; Rathbone, Michel
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9603125	A1	19960208	WO 1995-US10008	19950725

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ,

TM, TT
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 5447939	A	19950905	US 1994-280719	19940725
US 5801184	A	19980901	US 1995-488976	19950608
AU 9532775	A1	19960222	AU 1995-32775	19950725
AU 709454	B2	19990826		
EP 772440	A1	19970514	EP 1995-929408	19950725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
BR 9508339	A	19970930	BR 1995-8339	19950725
JP 10504814	T2	19980512	JP 1995-506010	19950725
FI 9700302	A	19970124	FI 1997-302	19970124
NO 9700312	A	19970127	NO 1997-312	19970124

PRIORITY APPLN. INFO.:

US 1994-280719	A	19940725
US 1995-488976	A	19950608
US 1995-492929	A	19950720
WO 1995-US10008	W	19950725

AB Methods and associated compns. and medicaments are disclosed which are directed generally to the control of cellular and neural activity and for selectively and controllably inducing the in vivo genetic expression of one or more naturally occurring genetically encoded mols. in mammals. More particularly, the present invention selectively activates or derepresses genes encoding for specific naturally occurring mols., e.g. proteins or neurotrophic factors, and induces the endogenous production of such naturally occurring compds. through the administration of carbon monoxide-dependent guanylyl cyclase modulating purine derivs. The methods of the invention may be used to affect a variety of cellular and neurol. functions and activities and to therapeutically or prophylactically treat a wide variety of neurodegenerative, neurol., cellular, and physiol. disorders. Evaluation of the effects of guanosine, 4-[(3-(1,6-dihydro-6-oxo-9-purin-9-yl)-1-oxopropyl)amino]benzoic acid (AIT-082), and inosine pranobex is included.

```
=> 140 or (pyrophospate or imidophosphate or imidodiphosphate)
            32 PYROPHOSPATE
             7 PYROPHOSPATES
            39 PYROPHOSPATE
               (PYROPHOSPATE OR PYROPHOSPATES)
           124 IMIDOPHOSPHATE
            40 IMIDOPHOSPHATES
           143 IMIDOPHOSPHATE
               (IMIDOPHOSPHATE OR IMIDOPHOSPHATES)
          1898 IMIDODIPHOSPHATE
            28 IMIDODIPHOSPHATES
          1904 IMIDODIPHOSPHATE
               (IMIDODIPHOSPHATE OR IMIDODIPHOSPHATES)
L53     174441 L40 OR (PYROPHOSPATE OR IMIDOPHOSPHATE OR IMIDODIPHOSPHATE)

=> l53 and (heme or peroxide)
         29679 HEME
          1925 HEMES
         30114 HEME
               (HEME OR HEMES)
        167047 PEROXIDE
         39554 PEROXIDES
        182714 PEROXIDE
               (PEROXIDE OR PEROXIDES)
L54       3610 L53 AND (HEME OR PEROXIDE)

=> l54 and acetylcholin?
         81231 ACETYLCHOLIN?
L55         11 L54 AND ACETYLCHOLIN?

=> l55 not l42
L56          1 L55 NOT L42

=> d l56 ibib abs

L56  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2002:682100  CAPLUS
TITLE:                   Inactivation of the human brain muscarinic
                         acetylcholine receptor by oxidative damage
                         catalyzed by a low molecular weight endogenous
                         inhibitor from Alzheimer's brain is prevented by
                         pyrophosphate analogs, bioflavonoids and other
                         antioxidants
AUTHOR(S):               Fawcett, John R.; Bordayo, Elizabeth Z.; Jackson,
                         Kathy; Liu, Howard; Peterson, Jennifer; Svitak, Aleta;
                         Frey, William H., II
CORPORATE SOURCE:        The Alzheimer's Research Center, Regions Hospital,
                         HealthPartners Research Foundation, St. Paul, MN,
                         55101-2595, USA
SOURCE:                  Brain Research (2002), 950(1,2), 10-20
                         CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER:               Elsevier Science B.V.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Oxidative stress has been implicated as a contributing factor to
     neurodegeneration in Alzheimer's disease.  An endogenous, low mol. weight
     (LMW) inhibitor from Alzheimer's brain inactivates the human brain
     muscarinic acetylcholine receptor (mAChR).  The inhibitor
     prevents agonist and antagonist binding to the mAChR as assesssed by
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radioligand binding studies. The LMW endogenous inhibitor, which has components with mol. wts. between 100 and 1000 Da, requires dissolved oxygen and glutathione. Prevention of inactivation of the mAChR with peroxidase suggests that the LMW endogenous inhibitor generates **peroxide**. **Heme**, previously shown to be present in the LMW endogenous inhibitor, also inactivates the mAChR in the presence of **peroxide**. Free radical damage to the muscarinic receptor by the endogenous inhibitor can be prevented through the use of naturally occurring antioxidants including bilirubin, biliverdin, carnosol, myricetin and quericetin. In addition, pyrophosphate, **imidodiphosphate**, bisphosphonates and related compds. also protect the muscarinic receptor from free radical damage. Inactivation of the mAChR by the LMW endogenous inhibitor is likely to be a factor in the continual decline of Alzheimer's patients, even those taking **acetylcholinesterase** inhibitors. Natural antioxidants and pyrophosphate analogs may improve the effectiveness of **acetylcholinesterase** inhibitors and prove useful in the treatment and prevention of Alzheimer's disease since the muscarinic **acetylcholine** receptor is required for memory, and decreased cholinergic function is a critical deficit in Alzheimer's disease.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d his l43-

     (FILE 'CAPLUS' ENTERED AT 09:15:23 ON 27 FEB 2003)

     FILE 'REGISTRY' ENTERED AT 09:18:11 ON 27 FEB 2003
               E "LEAD ION"/CN 25
L43            1 S E7

     FILE 'CAPLUS' ENTERED AT 09:18:43 ON 27 FEB 2003
L44         2151 S L43

     FILE 'REGISTRY' ENTERED AT 09:18:53 ON 27 FEB 2003
               E "LEAD CHLORIDE"/CN 25
L45            2 S E3

     FILE 'CAPLUS' ENTERED AT 09:19:38 ON 27 FEB 2003
L46         3304 S L45
L47         5419 L44 OR L46
L48           55 L40 AND L47
L49            2 L48 AND ACETYLCHOLIN?

=> d l49 total ibib abs

L49  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:107671  CAPLUS
DOCUMENT NUMBER:          136:163667
TITLE:                    Methods for biosensor library synthesis and
                          applications of use
INVENTOR(S):              Minshull, Jeremy; Davis, S. Christopher; Welch, Mark;
                          Raillard, Sun Ai; Vogel, Kurt; Krebber, Claus
PATENT ASSIGNEE(S):       Maxygen, Inc., USA
SOURCE:                   PCT Int. Appl., 158 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     WO 2002010750      A2   20020207       WO 2001-US24182   20010731
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
             RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
             UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2002102577      A1   20020801       US 2001-920452    20010731
     US 2002127623      A1   20020912       US 2001-920607    20010731
PRIORITY APPLN. INFO.:                   US 2000-222056P   P  20000731
                                         US 2000-244764P   P  20001031
AB   The invention concerns methods for sensing test stimuli using arrays of
     biopolymers. Reusable library arrays of biopolymers, such nucleic acid
     variants, and expression products encoded by nucleic acid variants are
     provided. The present invention provides novel methods for detecting a
     wide range of biol., chem. and biochem. stimuli. The methods of the
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invention utilize biopolymers and arrayed libraries of biopolymers, members of which are capable of binding the biol., chem. or biochem. stimuli, and upon binding produce a detectable signal. Upon contact with the test stimulus, a test stimulus array pattern is produced and detected. The test stimulus array pattern is then compared to the calibrating array pattern enabling identification of the test stimulus. Examples provide extensive listings of suitable hormones and enzymes suitable for such biosensor development. Diagrams describing the apparatus are given.

L49 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:816459 CAPLUS
DOCUMENT NUMBER: 135:339302
TITLE: Methods and compositions for enhancing cellular function through protection of tissue components
INVENTOR(S): Frey, William H., II; Fawcett, John Randall; Thorne, Robert Gary; Chen, Xueqing
PATENT ASSIGNEE(S): Healthpartners Research Foundation, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001082932	A2	20011108	WO 2001-US13931	20010430
WO 2001082932	A3	20020718		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002028786	A1	20020307	US 2001-844450	20010427
EP 1278525	A2	20030129	EP 2001-930957	20010430
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.:
US 2000-200843P P 20000501
US 2000-230263P P 20000906
US 2000-233025P P 20000915
US 2000-233263P P 20000918
WO 2001-US13931 W 20010430

OTHER SOURCE(S): MARPAT 135:339302

AB Methods and compns. for enhancing cellular function through protection of tissue components, such as receptors, proteins, lipids, nucleic acids, carbohydrates, hormones, vitamins, and cofactors, by administering pyrophosphate analogs or related compds. Preferably, the invention provides a method for protecting a muscarinic **acetylcholine** receptor (mAChR) an/or increasing the efficacy of and agent the directly or indirectly affects a mAChR in a subject in need thereof.

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=> d his l53-

     (FILE 'CAPLUS' ENTERED AT 09:38:12 ON 27 FEB 2003)
L53      174441 L40 OR (PYROPHOSPATE OR IMIDOPHOSPHATE OR IMIDODIPHOSPHATE)
L54        3610 L53 AND (HEME OR PEROXIDE)
L55          11 L54 AND ACETYLCHOLIN?
L56           1 L55 NOT L42
L57          55 L53 AND L47
L58           7 L57 AND (ACETYLCHOLIN? OR TOXIC? OR POISON?)
L59           0 L58 NOT (L49 OR L50)
L60           1 L57 AND (OXIDATIVE(W)STRESS)

     FILE 'STNGUIDE' ENTERED AT 09:48:15 ON 27 FEB 2003

     FILE 'CAPLUS' ENTERED AT 09:51:44 ON 27 FEB 2003
L61         908 L53 AND (OXIDATIVE(W)STRESS)
L62         272 L61 AND (HEME OR PEROXIDE)
L63         269 L62 NOT (L42 OR L52)
L64         201 L63 NOT PY>2000
L65         240 L63 NOT PY=2000
L66         173 L64 NOT PY=2000
L67          46 L66 AND (PHOSPHATE OR PYROPHOSPHATE OR IMIDOPHOSPHATE OR IMIDOD
L68           3 L63 AND (PYROPHOSPHATE OR IMIDOPHOSPHATE OR IMIDODIPHOSPHATE OR

=> d l68 total ibib abs

L68  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2002:682100  CAPLUS
TITLE:                   Inactivation of the human brain muscarinic
                         acetylcholine receptor by oxidative damage catalyzed
                         by a low molecular weight endogenous inhibitor from
                         Alzheimer's brain is prevented by
                         pyrophosphate analogs, bioflavonoids and other
                         antioxidants
AUTHOR(S):               Fawcett, John R.; Bordayo, Elizabeth Z.; Jackson,
                         Kathy; Liu, Howard; Peterson, Jennifer; Svitak, Aleta;
                         Frey, William H., II
CORPORATE SOURCE:        The Alzheimer's Research Center, Regions Hospital,
                         HealthPartners Research Foundation, St. Paul, MN,
                         55101-2595, USA
SOURCE:                  Brain Research (2002), 950(1,2), 10-20
                         CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER:               Elsevier Science B.V.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Oxidative stress has been implicated as a contributing
     factor to neurodegeneration in Alzheimer's disease.  An endogenous, low
     mol. weight (LMW) inhibitor from Alzheimer's brain inactivates the human
     brain muscarinic acetylcholine receptor (mAChR).  The inhibitor prevents
     agonist and antagonist binding to the mAChR as assesssed by radioligand
     binding studies.  The LMW endogenous inhibitor, which has components with
     mol. wts. between 100 and 1000 Da, requires dissolved oxygen and
     glutathione.  Prevention of inactivation of the mAChR with peroxidase
     suggests that the LMW endogenous inhibitor generates peroxide.
     Heme, previously shown to be present in the LMW endogenous
     inhibitor, also inactivates the mAChR in the presence of peroxide
     .  Free radical damage to the muscarinic receptor by the endogenous
     inhibitor can be prevented through the use of naturally occurring
     antioxidants including bilirubin, biliverdin, carnosol, myricetin and
```

quericetin. In addition, **pyrophosphate, imidodiphosphate**, bisphosphonates and related compds. also protect the muscarinic receptor from free radical damage. Inactivation of the mAChR by the LMW endogenous inhibitor is likely to be a factor in the continual decline of Alzheimer's patients, even those taking acetylcholinesterase inhibitors. Natural antioxidants and **pyrophosphate** analogs may improve the effectiveness of acetylcholinesterase inhibitors and prove useful in the treatment and prevention of Alzheimer's disease since the muscarinic acetylcholine receptor is required for memory, and decreased cholinergic function is a critical deficit in Alzheimer's disease.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L68 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:355892 CAPLUS

DOCUMENT NUMBER: 131:141866

TITLE: **Pyrophosphate** increases the efficiency of enterobactin-dependent iron uptake in Escherichia coli

AUTHOR(S): Perrotte-Piquemal, Marina; Danchin, Antoine; Biville, Francis

CORPORATE SOURCE: Unite Regulation de I'Expression Genetique, Dipartement de Biochimie et Genetique Moleculaire, Institut Pasteur, Paris, 75724, Fr.

SOURCE: Biochimie (1999), 81(3), 245-253
CODEN: BICMBE; ISSN: 0300-9084

PUBLISHER: Editions Scientifiques et Medicales Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Exogenous inorg. **pyrophosphate** increases the biomass yield of Escherichia coli. In this report, we show that the effect of **pyrophosphate** is related to iron uptake. We have found that addition of **pyrophosphate,** ammonium iron (III) citrate or iron (III) chloride, in M63 minimal medium containing 1.7 μM of iron, causes an increase in growth yield. In contrast to iron chloride or ammonium iron (III) citrate, exogenous **pyrophosphate** is deleterious to strains unable to synthesize enterobactin. Thus the pos. effect of **pyrophosphate** is related to the enterobactin uptake system expressed in a low iron content medium. **Pyrophosphate** in minimal medium has a repressing effect on the expression of Fur-regulated genes. In iron rich medium where enterobactin synthesis is strongly decreased, addition of **pyrophosphate** increases expression of Fur-regulated genes. Furthermore, this latter regulatory effect of **pyrophosphate** in iron-rich medium is enhanced in the absence of enterobactin synthesis. It has also been shown that addition of **pyrophosphate** protects the cell against the **oxidative stress** caused by the presence of hydrogen **peroxide** in an iron-rich containing medium. These results indicate that **pyrophosphate** acts as an iron-chelating agent, could trigger the enterobactin-dependent iron uptake system and could promote an increased binding of iron to enterobactin.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L68 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:591320 CAPLUS

DOCUMENT NUMBER: 129:300539

TITLE: Activation of iron regulatory protein-1 by **oxidative stress** in vitro

AUTHOR(S): Pantopoulos, Kostas; Hentze, Matthias W.

CORPORATE SOURCE: European Molecular Biology Laboratory, Heidelberg, D-69117, Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(18), 10559-10563
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Iron regulatory protein-1 (IRP-1), a central cytoplasmic regulator of cellular iron metabolism, is rapidly activated by **oxidative stress** to bind to mRNA iron-responsive elements. The authors have reconstituted the response of IRP-1 to extracellular H2O2 in a system derived from murine B6 fibroblasts permeabilized with streptolysin-O. This procedure allows separation of the cytosol from the remainder of the cells (cell pellet). IRP-1 in the cytosolic fraction fails to be directly activated by addition of H2O2. IRP-1 activation requires the presence of a nonsol., possibly membrane-associated component in the cell pellet. The streptolysin-O-based in vitro system faithfully recapitulates characteristic hallmarks of IRP-1 activation by H2O2 in intact cells. The authors show that the H2O2-mediated activation of IRP-1 is temperature dependent and sensitive to treatment with calf intestinal alkaline phosphatase (CIAP). Although IRP-1 activation is unaffected by addition of excess ATP or GTP to this in vitro system, it is neg. affected by the nonhydrolyzable nucleotide analogs adenylyl-**imidodiphosphate** and guanylyl-**imidophosphate** and completely blocked by ATP-γS and GTP-γS. The in vitro reconstitution of this **oxidative stress**-induced pathway has opened a different avenue for the biochem. dissection of the regulation of mammalian iron metabolism by **oxidative stress**. The data show that H2O2 must be sensed to stimulate a pathway to activate IRP-1.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> 163 and (pyrophosphate or imidophosphate or imidodiphosphate or etidron? or pamidron? or phosphate)

```
         35220 PYROPHOSPHATE
          3267 PYROPHOSPHATES
         36330 PYROPHOSPHATE
                 (PYROPHOSPHATE OR PYROPHOSPHATES)
           124 IMIDOPHOSPHATE
            40 IMIDOPHOSPHATES
           143 IMIDOPHOSPHATE
                 (IMIDOPHOSPHATE OR IMIDOPHOSPHATES)
          1898 IMIDODIPHOSPHATE
            28 IMIDODIPHOSPHATES
          1904 IMIDODIPHOSPHATE
                 (IMIDODIPHOSPHATE OR IMIDODIPHOSPHATES)
           449 ETIDRON?
           514 PAMIDRON?
        473454 PHOSPHATE
        104796 PHOSPHATES
        514791 PHOSPHATE
                 (PHOSPHATE OR PHOSPHATES)
L69        65 L63 AND (PYROPHOSPHATE OR IMIDOPHOSPHATE OR IMIDODIPHOSPHATE OR
              ETIDRON? OR PAMIDRON? OR PHOSPHATE)
```